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(54) **ALBUMIN VARIANTS**

(57) The present invention relates to variants of a parent albumin, the variants having altered plasma half-life compared with the parent albumin. The present invention also relates to polynucleotides encoding the variants; nucleic acid constructs, vectors, and host cells comprising the polynucleotides; and methods of using the variants.

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Description**Reference to a Sequence Listing**

5 **[0001]** This application contains a Sequence Listing in computer readable form, which is incorporated herein by reference.

Background of the Invention10 **Field of the Invention**

[0002] The invention relates to variants of albumin or fragments thereof or fusion polypeptides comprising variant albumin or fragments thereof having a change in binding affinity to FcRn and/or a change in half-life compared to the albumin, fragment thereof or fusion polypeptide comprising albumin or a fragment thereof. The invention allows tailoring of binding affinity and/or half-life of an albumin to the requirements and desires of a user or application.

Description of the Related Art

20 **[0003]** Albumin is a protein naturally found in the blood plasma of mammals where it is the most abundant protein. It has important roles in maintaining the desired osmotic pressure of the blood and also in transport of various substances in the blood stream. Albumins have been characterized from many species including human, pig, mouse, rat, rabbit and goat and they share a high degree of sequence and structural homology.

25 **[0004]** Albumin binds *in vivo* to its receptor, the neonatal Fc receptor (FcRn) "Brambell" and this interaction is known to be important for the plasma half-life of albumin. FcRn is a membrane bound protein, expressed in many cell and tissue types. FcRn has been found to salvage albumin from intracellular degradation (Roopenian D. C. and Akilesh, S. (2007), Nat. Rev. Immunol 7, 715-725.). FcRn is a bifunctional molecule that contributes to maintaining a high level of IgGs and albumin in serum in mammals such as human beings.

30 **[0005]** Whilst the FcRn-immunoglobulin (IgG) interaction has been characterized in the prior art, the FcRn-albumin interaction is less well characterized. The major FcRn binding site is localized within DIII (381-585), (Andersen et al (2010), Clinical Biochemistry 43,367-372). A number of key amino acids have been shown to be important in binding, notably histidines H464, H510 and H536 and Lys500 (Andersen et al (2010), Nat. Commun. 3:610. DOI:10.1038/ncomms1607). Data indicates that IgG and albumin bind non-cooperatively to distinct sites on FcRn (Andersen et al. (2006), Eur. J. Immunol 36, 3044-3051; Chaudhury et al. (2006), Biochemistry 45, 4983-4990.).

35 **[0006]** It is known that mouse FcRn binds IgG from mice and humans whereas human FcRn appears to be more discriminating (Ober et al. (2001) Int. Immunol 13, 1551-1559). Andersen et al. (2010) Journal of Biological Chemistry 285(7):4826-36, describes the affinity of human and mouse FcRn for each mouse and human albumin (all possible combinations). No binding of albumin from either species was observed at physiological pH to either receptor. At acidic pH, a 100-fold difference in binding affinity was observed. In all cases, binding of albumin and IgG from either species to both receptors were additive.

40 **[0007]** Human serum albumin (HSA) has been well characterized as a polypeptide of 585 amino acids, the sequence of which can be found in Peters, T., Jr. (1996) All about Albumin: Biochemistry, Genetics and Medical, Applications pp10, Academic Press, Inc., Orlando (ISBN 0-12-552110-3). It has a characteristic binding to its receptor FcRn, where it binds at pH 6.0 but not at pH 7.4.

45 **[0008]** The plasma half-life of HSA has been found to be approximately 19 days. A natural variant having lower plasma half-life has been identified (Peach, R. J. and Brennan, S. O., (1991) Biochim Biophys Acta.1097:49-54) having the substitution D494N. This substitution generated an N-glycosylation site in this variant, which is not present in the wild-type albumin. It is not known whether the glycosylation or the amino acid change is responsible for the change in plasma half-life.

50 **[0009]** Albumin has a long plasma half-life and because of this property it has been suggested for use in drug delivery. Albumin has been conjugated to pharmaceutically beneficial compounds (WO2000/69902), and it was found that the conjugate maintained the long plasma half-life of albumin. The resulting plasma half-life of the conjugate was generally considerably longer than the plasma half-life of the beneficial therapeutic compound alone.

55 **[0010]** Further, albumin has been genetically fused to therapeutically beneficial peptides (WO 2001/79271 A and WO2003/59934) with the typical result that the fusion has the activity of the therapeutically beneficial peptide and a considerably longer plasma half-life than the plasma half-life of the therapeutically beneficial peptides alone.

[0011] Otagiri et al (2009), Biol. Pharm. Bull. 32(4), 527-534, discloses more than 70 albumin variants, of these 25 of these are found to be mutated in domain III. A natural variant lacking the last 175 amino acids at the carboxy termini has been shown to have reduced half-life (Andersen et al (2010), Clinical Biochemistry 43, 367-372). Iwao *et al* (2007)

studied the half-life of naturally occurring human albumin variants using a mouse model, and found that K541E and K560E had reduced half-life, E501K and E570K had increased half-life and K573E had almost no effect on half-life (Iwao, et. al. (2007) B.B.A. Proteins and Proteomics 1774, 1582-1590). Galliano et al (1993) Biochim. Biophys. Acta 1225, 27-32 discloses a natural variant E505K. Minchiotti *et al* (1990) discloses a natural variant K536E. Minchiotti et al (1987) Biochim. Biophys. Acta 916, 411-418, discloses a natural variant K574N. Takahashi et al (1987) Proc. Natl. Acad. Sci. USA 84, 4413-4417, discloses a natural variant D550G. Carlson et al (1992). Proc. Nat. Acad. Sci. USA 89, 8225- 8229, discloses a natural variant D550A.

[0012] WO2011/051489 and WO 2012/150319 (PCT/EP2012/058206) disclose a number of point mutations in albumin which modulate the binding of albumin to FcRn, WO2010/092135 discloses a number of point mutations in albumin which increase the number of thiols available for conjugation in the albumin, the disclosure is silent about the effect of the mutations on the binding of the albumin to FcRn. WO2011/103076 discloses albumin variants, each containing a substitution in Domain III of HSA. WO2012/112188 discloses albumin variants containing substitutions in Domain III of HSA.

[0013] Albumin has the ability to bind a number of ligands and these become associated (associates) with albumin. This property has been utilized to extend the plasma half-life of drugs having the ability to non-covalently bind to albumin. This can also be achieved by binding a pharmaceutical beneficial compound, which has little or no albumin binding properties, to a moiety having albumin binding properties, see review article and reference therein, Kratz (2008) Journal of Controlled Release 132, 171-183.

[0014] Albumin is used in preparations of pharmaceutically beneficial compounds, in which such a preparation maybe for example, but not limited to, a nanoparticle or microparticle of albumin. In these examples the delivery of a pharmaceutically beneficial compound or mixture of compounds may benefit from alteration in the albumin's affinity to its receptor where the beneficial compound has been shown to associate with albumin for the means of delivery. It is not clear what determines the plasma half-life of the formed associates (for example but not limited to Levemir®, Kurtzhals P et al. Biochem. J. 1995; 312:725-731), conjugates or fusion polypeptides but it appears to be a result of the combination of the albumin and the selected pharmaceutically beneficial compound/polypeptide. It would be desirable to be able to control the plasma half-life of given albumin conjugates, associates or albumin fusion polypeptides so that a longer or shorter plasma half-life can be achieved than given by the components of the association, conjugation or fusion, in order to be able to design a particular drug according to the particulars of the indication intended to be treated.

[0015] Albumin is known to accumulate and be catabolized in tumors; it has also been shown to accumulate in inflamed joints of rheumatoid arthritis sufferers. See review article and reference therein, Kratz (2008) Journal of Controlled Release 132, 171-183. It is envisaged that HSA variants with increased affinity for FcRn would be advantageous for the delivery of pharmaceutically beneficial compounds.

[0016] It may even be desirable to have variants of albumin that have little or no binding to FcRn in order to provide shorter half-lives or controlled serum pharmacokinetics as described by Kenanova *et al* (2009) *J. Nucl. Med.*; **50** (Supplement 2):1582).

[0017] Kenanova et al (2010, Protein Engineering, Design & Selection 23(10): 789-798; WO2010/118169) discloses a docking model comprising a structural model of domain III of HSA (solved at pH 7 to 8) and a structural model of FcRn (solved at pH 6.4). Kenanova *et al* discloses that positions 464, 505, 510, 531 and 535 in domain III potentially interact with FcRn. The histidines at positions 464, 510 and 535 were identified as being of particular interest by Chaudhury *et al.*, (2006, *op. cit.*) and these were shown to have a significant reduction in affinity and shorter half-life in mouse by Kenanova (2010, *op. cit.*). However, the studies of Kenanova *et al* are limited to domain III of HSA and therefore do not consider HSA in its native intact configuration. Furthermore, the identified positions result in a decrease in affinity for the FcRn receptor.

[0018] The present invention provides further variants having modulated (i.e. altered) binding affinity to the FcRn receptor. The albumin moiety or moieties may therefore be used to tailor the binding affinity to FcRn and/or half-life of fusion polypeptides, conjugates, associates, nanoparticles and compositions comprising the albumin moiety.

Summary of the Invention

[0019] The present invention relates to albumin variants comprising one or more (several) alterations in Domain I and one or more (several) alterations in Domain III of the mature polypeptide of SEQ ID NO: 2 or equivalent positions of other albumins or fragments thereof.

[0020] The present invention also relates to albumin variants comprising one or more (several) alterations in Domain I of the mature polypeptide of SEQ ID NO: 2 or equivalent positions of other albumins or fragments thereof.

[0021] The present invention also relates to albumin variants comprising one or more (several) alterations in Domain III of the mature polypeptide of SEQ ID NO: 2 or equivalent positions of other albumins or fragments thereof.

[0022] The present invention also relates to isolated polynucleotides encoding the variants; nucleic acid constructs, vectors, and host cells comprising the polynucleotides; and methods of producing the variants.

[0023] The invention also relates to conjugates or associates comprising the variant albumin or fragment thereof according to the invention and a beneficial therapeutic moiety or to a fusion polypeptide comprising a variant albumin or fragment thereof of the invention and a fusion partner polypeptide.

[0024] The invention further relates to compositions comprising the variant albumin, fragment thereof, fusion polypeptide comprising variant albumin or fragment thereof or conjugates comprising the variant albumin or fragment thereof, according to the invention or associates comprising the variant albumin or fragment thereof, according to the invention. The compositions are preferably pharmaceutical compositions.

[0025] The invention further relates to a pharmaceutical composition comprising a variant albumin, fragment thereof, fusion polypeptide comprising variant albumin or fragment thereof or conjugates comprising the variant albumin or fragment thereof, or associates comprising the variant albumin or fragment thereof.

[0026] The invention also relates to the use of the variants, fragments, fusion polypeptides, conjugates, associates, nanoparticles and microparticles.

[0027] The invention also relates to a method for preparing a variant albumin, fragment thereof, fusion polypeptide comprising variant albumin or fragment thereof or conjugates comprising the variant albumin or fragment thereof, or associates comprising the variant albumin or fragment thereof.

Brief Description of the Figures

[0028]

Figure 1: Multiple alignment of amino acid sequences of (i) full length mature HSA (Hu_1_2_3), (ii) an albumin variant comprising domain I and domain III of HSA (Hu_1_3), (iii) an albumin variant comprising domain II and domain III of HSA (Hu_2_3), (iv) full-length *Macaca mulatta* albumin (Mac_mul), (v) full-length *Rattus norvegicus* albumin (Rat) and (vi) full-length *Mus musculus* albumin (Mouse). Positions 500, 550 and 573 (relative to full length HSA) are indicated by arrows. In Figure 1 Domains I, II and III are referred to as 1, 2 and 3 (respectively).

Figure 2: Multiple alignment of amino acid sequence of mature albumin from human, sheep, mouse, rabbit and goat and immature albumins from chimpanzee ("Chimp"), macaque, hamster, guinea pig, rat, cow, horse, donkey, dog, chicken, and pig. The Start and End amino acids of domains 1, 2 and 3 (as defined by Dockal et al (The Journal of Biological Chemistry, 1999, Vol. 274(41): 29303-29310)) are indicated with respect to mature human albumin.

Figure 3: Conserved groups of amino acids based on their properties.

Figure 4: Representation of shFcRn-HSA docking model. (A-B) Two orientations of the complex are shown. Albumin is shown by a space-filling diagram, FcRn is shown as a ribbon diagram. The core binding interface of HSA is highlighted in pink (in grey-scale this is seen as the darkest (almost black) region; DI (CBI)), while the area distally localized from the interface is shown as DII (orange) and DIII is split into sub-domains DIIIa (in colour, this is cyan) and DIIIb (in colour, this is blue).

Figure 5: shFcRn binding of WT HSA, HSA K573P and HSA N111Q/K573P at pH5.5, samples were injected over immobilized shFcRn-HIS (-1500-2500 RU) at pH 5.5.

Figure 6: A proposed shFcRn-HSA docking model, showing the spatial relationship between shFcRn (space filling diagram) and HSA (ribbon diagram) DI, DII and DIII including loops of HSA comprising positions 78 to 88 and 108 to 112.

Definitions

[0029] Variant: The term "variant" means a polypeptide derived from a parent albumin by one or more (several) alteration(s), i.e., a substitution, insertion, and/or deletion, at one or more (several) positions. A substitution means a replacement of an amino acid occupying a position with a different amino acid; a deletion means removal of an amino acid occupying a position; and an insertion means adding 1 or more (several), such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1 to 3 amino acids immediately adjacent an amino acid occupying a position. In relation to substitutions, 'immediately adjacent' may be to the N-side ('upstream') or C-side ('downstream') of the amino acid occupying a position ('the named amino acid'). Therefore, for an amino acid named/numbered 'X', the insertion may be at position 'X+1' ('downstream') or at position 'X-1' ('upstream').

[0030] Mutant: The term "mutant" means a polynucleotide encoding a variant.

[0031] Wild-Type Albumin: The term "wild-type" (WT) albumin means albumin having the same amino acid sequence as naturally found in an animal or in a human being.

[0032] Parent Albumin: The term "parent" or "parent albumin" means an albumin to which an alteration is made by the hand of man to produce the albumin variants of the invention. The parent may be a naturally occurring (wild-type) polypeptide or an allele thereof, or even a variant thereof.

[0033] Albumin: Albumins are proteins and constitute the most abundant protein in plasma in mammals and albumins

from a long number of mammals have been characterized by biochemical methods and/or by sequence information. Several albumins, e.g., human serum albumin (HSA), have also been characterized crystallographically and the structure determined (HSA: He XM, Carter DC (July 1992). "Atomic structure and chemistry of human serum albumin". Nature 358 (6383): 209-15; horse albumin: Ho, J.X. et al. (2001). X-ray and primary structure of horse serum albumin (*Equus caballus*) at 0.27-nm resolution. Eur J Biochem. 215(1):205-12).

[0034] The term "albumin" means a protein having the same and/or very similar three dimensional (tertiary) structure as HSA or HSA domains and has similar properties to HSA or to the relevant domains. Similar three dimensional structures are for example the structures of the albumins from the species mentioned herein. Some of the major properties of albumin are i) its ability to regulate plasma volume (oncotic activity), ii) a long plasma half-life of around 19 days $\pm$ 5 days, iii) binding to FcRn, iv) ligand-binding, e.g. binding of endogenous molecules such as acidic, lipophilic compounds including bilirubin, fatty acids, hemin and thyroxine (see also Table 1 of Kragh-Hansen et al, 2002, Biol. Pharm. Bull. 25, 695, hereby incorporated by reference), v) binding of small organic compounds with acidic or electronegative features e.g. drugs such as warfarin, diazepam, ibuprofen and paclitaxel (see also Table 1 of Kragh-Hansen et al, 2002, Biol. Pharm. Bull. 25, 695, hereby incorporated by reference). Not all of these properties need to be fulfilled in order to characterize a protein or fragment as an albumin. If a fragment, for example, does not comprise a domain responsible for binding of certain ligands or organic compounds the variant of such a fragment will not be expected to have these properties either.

[0035] Albumins have generally a long plasma half-life of approximately 20 days or longer, e.g., HSA has a plasma half-life of 19 days. It is known that the long plasma half-life of HSA is mediated via interaction with its receptor FcRn, however, an understanding or knowledge of the exact mechanism behind the long half-life of HSA is not essential for the invention.

[0036] As examples of albumin proteins according to the invention can be mentioned human serum albumin (e.g. AAA98797 or P02768-1, SEQ ID NO: 2 (mature), SEQ ID NO: 4 (immature)), primate serum albumin, (such as chimpanzee serum albumin (e.g. predicted sequence XP_517233.2 SEQ ID NO: 5), gorilla serum albumin or macaque serum albumin (e.g. NP_001182578, SEQ ID NO: 6), rodent serum albumin (such as hamster serum albumin (e.g. A6YF56, SEQ ID NO: 7), guinea pig serum albumin (e.g. Q6WDN9-1, SEQ ID NO: 8), mouse serum albumin (e.g. AAH49971 or P07724-1 Version 3, SEQ ID NO: 9) and rat serum albumin (e.g. AAH85359 or P02770-1 Version 2, SEQ ID NO: 10))), bovine serum albumin (e.g. cow serum albumin P02769-1, SEQ ID NO: 11), equine serum albumin such as horse serum albumin (e.g. P35747-1, SEQ ID NO: 12) or donkey serum albumin (e.g. Q5XLE4-1, SEQ ID NO: 13), rabbit serum albumin (e.g. P49065-1 Version 2, SEQ ID NO: 14), goat serum albumin (e.g. ACF10391, SEQ ID NO: 15), sheep serum albumin (e.g. P14639-1, SEQ ID NO: 16), dog serum albumin (e.g. P49822-1, SEQ ID NO: 17), chicken serum albumin (e.g. P19121-1 Version 2, SEQ ID NO: 18) and pig serum albumin (e.g. P08835-1 Version 2, SEQ ID NO: 19) or a polypeptide having at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98 or at least 99% amino acid identity to such an albumin. The parent or reference albumin may be an artificial variant such as HSA K573P (SEQ ID NO: 3) or a chimeric albumin such as the N-terminal of HSA and the C-terminal of macaca albumin (SEQ ID NO: 20), N-terminal of HSA and the C-terminal of mouse albumin (SEQ ID NO: 21), N-terminal of HSA and the C-terminal of rabbit albumin (SEQ ID NO: 22), N-terminal of HSA and the C-terminal of sheep albumin (SEQ ID NO: 23).

[0037] Other examples of albumin, which are also included in the scope of this application, include ovalbumin (e.g. P01012.pro: chicken ovalbumin; O73860.pro: turkey ovalbumin).

[0038] HSA as disclosed in SEQ ID NO: 2 or any naturally occurring allele thereof, is the preferred albumin (parent albumin) according to the invention. HSA is a protein consisting of 585 amino acid residues and has a molecular weight of 67 kDa. In its natural form it is not glycosylated. The skilled person will appreciate that natural alleles may exist having essentially the same properties as HSA but having one or more (several) amino acid changes compared to SEQ ID NO: 2, and the inventors also contemplate the use of such natural alleles as parent albumin according to the invention.

[0039] The parent albumin, a fragment thereof, or albumin part of a fusion polypeptide comprising albumin or a fragment thereof according to the invention preferably has a sequence identity to the sequence of HSA shown in SEQ ID NO: 2 of at least 60%, preferably at least 70%, preferably at least 80%, preferably at least 85%, preferably at least 86%, preferably at least 87%, preferably at least 88%, preferably at least 89%, preferably at least 90%, preferably at least 91%, preferably at least 92%, preferably at least 93%, preferably at least 94%, preferably at least 95%, more preferred at least 96%, more preferred at least 97%, more preferred at least 98% and most preferred at least 99%. It is preferred that the parent albumin maintains at least one of the major properties of albumin or a similar tertiary structure as an albumin, such as HSA. The sequence identity may be over the full-length of SEQ ID NO: 2 or over a molecule consisting of or comprising a fragment such as one or more (several) domains of SEQ ID NO: 2 such as a molecule consisting of or comprising domain III (e.g. SEQ ID NO: 27), a molecule consisting of or comprising domain II and domain III (e.g. SEQ ID NO: 25), a molecule consisting of or comprising domain I and domain III (e.g. SEQ ID NO: 24), a molecule consisting of or comprising two copies of domain III (e.g. SEQ ID NO: 26), a molecule consisting of or comprising three copies of domain III (e.g. SEQ ID NO: 28) or a molecule consisting of or comprising domain I and two copies of domain III (e.g. SEQ ID NO: 29).

[0040] The parent preferably comprises or consists of the amino acid sequence of SEQ ID NO: 4 (immature sequence of HSA) or SEQ ID NO: 2 (mature sequence of HSA).

[0041] In another embodiment, the parent is an allelic variant of the mature polypeptide of SEQ ID NO: 2.

[0042] The parent albumin may be encoded by a polynucleotide that hybridizes under very low stringency conditions, low stringency conditions, medium stringency conditions, medium-high stringency conditions, high stringency conditions, or very high stringency conditions with (i) the mature polypeptide coding sequence of SEQ ID NO: 1, or (ii) the full-length complementary strand of (i) (J. Sambrook, E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning, A Laboratory Manual, 2d edition, Cold Spring Harbor, New York).

[0043] The polynucleotide of SEQ ID NO: 1 or a subsequence thereof, as well as the amino acid sequence of SEQ ID NO: 2 or a fragment thereof, may be used to design nucleic acid probes to identify and clone DNA encoding a parent from strains of different genera or species according to methods well known in the art. In particular, such probes can be used for hybridization with the genomic or cDNA of the genus or species of interest, following standard Southern blotting procedures, in order to identify and isolate the corresponding gene therein. Such probes can be considerably shorter than the entire sequence, but should be at least 14, e.g., at least 25, at least 35, or at least 70 nucleotides in length. Preferably, the nucleic acid probe is at least 100 nucleotides in length, e.g., at least 200 nucleotides, at least 300 nucleotides, at least 400 nucleotides, at least 500 nucleotides, at least 600 nucleotides, at least 700 nucleotides, at least 800 nucleotides, or at least 900 nucleotides in length. Both DNA and RNA probes can be used. The probes are typically labelled for detecting the corresponding gene (for example, with ³²P, ³H, ³⁵S, biotin, or avidin). Such probes are encompassed by the invention.

[0044] A genomic DNA or cDNA library prepared from such other organisms may be screened for DNA that hybridizes with the probes described above and encodes a parent. Genomic or other DNA from such other organisms may be separated by agarose or polyacrylamide gel electrophoresis, or other separation techniques. DNA from the libraries or the separated DNA may be transferred to and immobilized on nitrocellulose or other suitable carrier material. In order to identify a clone or DNA that is homologous with SEQ ID NO: 1 or a subsequence thereof, the carrier material is used in a Southern blot.

[0045] For purposes of the invention, hybridization indicates that the polynucleotide hybridizes to a labelled nucleotide probe corresponding to the polynucleotide shown in SEQ ID NO: 1, its complementary strand, or a subsequence thereof, under low to very high stringency conditions. Molecules to which the probe hybridizes can be detected using, for example, X-ray film or any other detection means known in the art.

[0046] The nucleic acid probe may comprise or consist of the mature polypeptide coding sequence of SEQ ID NO: 1, i.e. nucleotides 1 to 1785 of SEQ ID NO: 1. The nucleic acid probe may comprise or consist of a polynucleotide that encodes the polypeptide of SEQ ID NO: 2 or a fragment thereof.

[0047] For long probes of at least 100 nucleotides in length, very low to very high stringency conditions are defined as pre-hybridization and hybridization at 42°C in 5X SSPE, 0.3% SDS, 200 micrograms/ml sheared and denatured salmon sperm DNA, and either 25% formamide for very low and low stringencies, 35% formamide for medium and medium-high stringencies, or 50% formamide for high and very high stringencies, following standard Southern blotting procedures for 12 to 24 hours optimally. The carrier material is finally washed three times each for 15 minutes using 2X SSC, 0.2% SDS at 45°C (very low stringency), 50°C (low stringency), 55°C (medium stringency), 60°C (medium-high stringency), 65°C (high stringency), or 70°C (very high stringency).

[0048] For short probes that are about 15 nucleotides to about 70 nucleotides in length, stringency conditions are defined as pre-hybridization and hybridization at about 5°C to about 10°C below the calculated T_m using the calculation according to Bolton and McCarthy (1962, Proc. Natl. Acad. Sci. USA 48: 1390) in 0.9 M NaCl, 0.09 M Tris-HCl pH 7.6, 6 mM EDTA, 0.5% NP-40, 1X Denhardt's solution, 1 mM sodium pyrophosphate, 1 mM sodium monobasic phosphate, 0.1 mM ATP, and 0.2 mg of yeast RNA per ml following standard Southern blotting procedures for 12 to 24 hours optimally. The carrier material is finally washed once in 6X SSC plus 0.1% SDS for 15 minutes and twice each for 15 minutes using 6X SSC at 5°C to 10°C below the calculated T_m .

[0049] The parent may be encoded by a polynucleotide with a sequence identity to the mature polypeptide coding sequence of SEQ ID NO: 1 of at least 60%, e.g., at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, which encodes a polypeptide which is able to function as an albumin. In an embodiment, the parent is encoded by a polynucleotide comprising or consisting of SEQ ID NO: 1.

[0050] Albumin moiety: The albumin part of a fusion polypeptide, conjugate, associate, nanoparticle or composition comprising the albumin variant or fragment thereof according to the invention, may be referred to as an 'albumin moiety' or 'albumin component'. A polypeptide according to the invention may comprise or consist of an albumin moiety.

[0051] FcRn and shFcRn: The term "FcRn" means the human neonatal Fc receptor (FcRn). shFcRn is a soluble recombinant form of FcRn. hFcRn is a heterodimer of SEQ ID NO: 30 (truncated heavy chain of the major histocompatibility complex class I-like Fc receptor (FCGRT)) and SEQ ID NO: 31 (beta-2-microglobulin). Together, SEQ ID NO: 30 and 31 form hFcRn.

[0052] Isolated variant: The term "isolated variant" means a variant that is modified by the hand of man and separated completely or partially from at least one component with which it naturally occurs. The term "isolated variant" means a variant in a form or environment which does not occur in nature. Non-limiting examples of isolated substances include (1) any non-naturally occurring variant, (2) any variant that is at least partially removed from one or more (several) or all of the naturally occurring constituents with which it is associated in nature; (3) any variant modified by the hand of man relative to the polypeptide from which it is derived (e.g. the polypeptide from which it is derived as found in nature); or (4) any variant modified by increasing the amount of the variant e relative to other components with which it is naturally associated (e.g., multiple copies of a gene encoding the substance; use of a stronger promoter than the promoter naturally associated with the gene encoding the substance). An isolated variant may be present in a fermentation broth sample. The variant may be at least 1% pure, e.g., at least 5% pure, at least 10% pure, at least 20% pure, at least 40% pure, at least 60% pure, at least 80% pure, and at least 90% pure, as determined by SDS-PAGE or GP-HPLC.

[0053] Substantially pure variant: The term "substantially pure variant" means a preparation that contains at most 10%, at most 8%, at most 6%, at most 5%, at most 4%, at most 3%, at most 2%, at most 1%, and at most 0.5% by weight of other polypeptide material with which it is natively or recombinantly associated. Preferably, the variant is at least 92% pure, e.g., at least 94% pure, at least 95% pure, at least 96% pure, at least 97% pure, at least 98% pure, at least 99%, at least 99.5% pure, and 100% pure by weight of the total polypeptide material present in the preparation. Purity may be determined by SDS-PAGE or GP-HPLC. The variants of the invention are preferably in a substantially pure form. This can be accomplished, for example, by preparing the variant by well-known recombinant methods and by purification methods.

[0054] Mature polypeptide: The term "mature polypeptide" means a polypeptide in its final form following translation and any post-translational modifications, such as N-terminal processing, C-terminal truncation, glycosylation, phosphorylation, etc. The mature polypeptide may be amino acids 1 to 585 of SEQ ID NO: 2, e.g. with alterations according to the invention and/or with the inclusion of any post-translational modifications.

[0055] Mature polypeptide coding sequence: The term "mature polypeptide coding sequence" means a polynucleotide that encodes a mature albumin polypeptide. The mature polypeptide coding sequence may be nucleotides 1 to 1758 of SEQ ID NO: 1 e.g. with inclusions required to encode a variant according to the invention.

[0056] Sequence Identity: The relatedness between two amino acid sequences or between two nucleotide sequences is described by the parameter "sequence identity".

[0057] For purposes of the invention, the degree of sequence identity between two amino acid sequences is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 3.0.0 or later, more preferably version 5.0.0 or later. The optional parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EBLOSUM62 (EMBOSS version of BLOSUM62) substitution matrix. The output of Needle labelled "longest identity" (obtained using the -nobrief option) is used as the percent identity and is calculated as follows:

$$(\text{Identical Residues} \times 100) / (\text{Length of Alignment} - \text{Total Number of Gaps in Alignment})$$

[0058] For purposes of the invention, the degree of sequence identity between two deoxyribonucleotide sequences is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, *supra*) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, *supra*), preferably version 3.0.0 or later, more preferably version 5.0.0 or later. The optional parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EDNAFULL (EMBOSS version of NCBI NUC4.4) substitution matrix. The output of Needle labelled "longest identity" (obtained using the -nobrief option) is used as the percent identity and is calculated as follows:

$$(\text{Identical Deoxyribonucleotides} \times 100) / (\text{Length of Alignment} - \text{Total Number of Gaps in Alignment})$$

[0059] Fragment: The term "fragment" means a polypeptide having one or more (several) amino acids deleted from the amino and/or carboxyl terminus of an albumin and/or an internal region of albumin that has retained the ability to bind to FcRn. Fragments may consist of one uninterrupted sequence derived from HSA or it may comprise two or more (several) sequences derived from HSA. The fragments according to the invention have a size of more than approximately 20 amino acid residues, preferably more than 30 amino acid residues, more preferred more than 40 amino acid residues, more preferred more than 50 amino acid residues, more preferred more than 75 amino acid residues, more preferred more than 100 amino acid residues, more preferred more than 200 amino acid residues, more preferred more than 300 amino acid residues, even more preferred more than 400 amino acid residues and most preferred more than 500 amino

acid residues. A fragment may comprise or consist of one more domains of albumin such as DI + DII, DI + DIII, DII + DIII, DIII + DIII, DI + DIII + DIII, DIII + DIII + DIII, or fragments of such domains or combinations of domains.

[0060] Domains I, II and III may be defined with reference to HSA (SEQ ID NO: 2). For example, HSA domain I may consist of or comprise amino acids 1 to 194 (± 1 to 15 amino acids) of SEQ ID NO: 2, HSA domain II may consist of or comprise amino acids 189 to 385 (± 1 to 15 amino acids) of SEQ ID NO: 2 and domain III may consist of or comprise amino acid residues 381 to 585 (± 1 to 15 amino acids) of SEQ ID NO: 2. " ± 1 to 15 amino acids" means that the residue number may deviate by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids to the C-terminus and/or to the N-terminus of the stated amino acid position. Examples of domains I, II and III are described by Dockal et al (The Journal of Biological Chemistry, 1999, Vol. 274(41): 29303-29310) and Kjeldsen et al (Protein Expression and Purification, 1998, Vol 13: 163-169) and are tabulated below.

Amino acid residues of HSA domains I, II and III with reference to SEQ ID NO: 2	Dockal et al	Kjeldsen et al
Domain I	1 to 197	1 to 192
Domain II	189 to 385	193 to 382
Domain III	381 to 585	383 to 585

[0061] The skilled person can identify domains I, II and III in non-human albumins by amino acid sequence alignment with HSA, for example using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 3.0.0 or later, more preferably version 5.0.0 or later. The optional parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EBLOSUM62 (EMBOSS version of BLOSUM62) substitution matrix. Other suitable software includes MUSCLE ((Multiple sequence comparison by log-expectation, Robert C. Edgar, Version 3.6, <http://www.drive5.com/muscle>; Edgar (2004) Nucleic Acids Research 32(5), 1792-97 and Edgar (2004) BMC Bioinformatics, 5(1): 113) which may be used with the default settings as described in the User Guide (Version 3.6, September 2005). Versions of MUSCLE later than 3.6 may also be used for any aspect of the invention). Examples of suitable alignments are provided in Figures 1 and 2.

[0062] It is preferred that domains have at least 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, 99.5 % identity or 100% identity to Domain I, II or III of HSA (SEQ ID NO: 2).

[0063] Allelic variant: The term "allelic variant" means any of two or more (several) alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequences. An allelic variant of a polypeptide is a polypeptide encoded by an allelic variant of a gene.

[0064] Coding sequence: The term "coding sequence" means a polynucleotide, which directly specifies the amino acid sequence of its translated polypeptide product. The boundaries of the coding sequence are generally determined by an open reading frame, which usually begins with the ATG start codon or alternative start codons such as GTG and TTG and ends with a stop codon such as TAA, TAG, and TGA. The coding sequence may be a DNA, cDNA, synthetic, or recombinant polynucleotide.

[0065] cDNA: The term "cDNA" means a DNA molecule that can be prepared by reverse transcription from a mature, spliced, mRNA molecule obtained from a eukaryotic cell. cDNA lacks intron sequences that may be present in the corresponding genomic DNA. The initial, primary RNA transcript is a precursor to mRNA that is processed through a series of steps, including splicing, before appearing as mature spliced mRNA.

[0066] Nucleic acid construct: The term "nucleic acid construct" means a nucleic acid molecule, either single- or double-stranded, which is isolated from a naturally occurring gene or is modified to contain segments of nucleic acids in a manner that would not otherwise exist in nature or which is synthetic. The term nucleic acid construct is synonymous with the term "expression cassette" when the nucleic acid construct contains the control sequences required for expression of a coding sequence of the invention.

[0067] Control sequences: The term "control sequences" means all components (e.g. nucleic acid sequences) necessary for the expression of a polynucleotide encoding a variant of the invention. Each control sequence may be native (i.e. from the same gene) or foreign (i.e. from a different gene) to the polynucleotide encoding the variant or native or foreign to each other. Such control sequences include, but are not limited to, a leader, polyadenylation sequence, propeptide sequence, promoter, signal peptide sequence, and transcription terminator. At a minimum, the control sequences include a promoter, and transcriptional and translational stop signals. The control sequences may be provided with linkers for the purpose of introducing specific restriction sites facilitating ligation of the control sequences within the coding region of the polynucleotide encoding a variant.

[0068] Operably linked: The term "operably linked" means a configuration in which a control sequence is placed at an appropriate position relative to the coding sequence of a polynucleotide such that the control sequence directs the expression of the coding sequence.

[0069] Expression: The term "expression" includes any step involved in the production of the variant including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion.

[0070] Expression vector: The term "expression vector" means a linear or circular DNA molecule that comprises a polynucleotide encoding a variant and is operably linked to additional nucleotides (e.g. control sequences) that provide for its expression.

[0071] Host cell: The term "host cell" means any cell type that is susceptible to transformation, transfection, transduction, and/or the like with a nucleic acid construct or expression vector comprising a polynucleotide of the present invention. The term "host cell" encompasses any progeny of a parent cell that is not identical to the parent cell due to mutations that occur during replication.

[0072] Plasma half-life: Plasma half-life is ideally determined *in vivo* in suitable individuals. However, since it is time consuming and expensive and there inevitable are ethical concerns connected with doing experiments in animals or man it is desirable to use an *in vitro* assay for determining whether plasma half-life is extended or reduced. It is known that the binding of albumin to its receptor FcRn is important for plasma half-life and the correlation between receptor binding and plasma half-life is that a higher affinity of albumin to its receptor leads to longer plasma half-life. Thus for the invention a higher affinity of albumin to FcRn is considered indicative of an increased plasma half-life and a lower affinity of albumin to its receptor is considered indicative of a reduced plasma half-life.

[0073] In this application and claims the binding of albumin to its receptor FcRn is described using the term affinity and the expressions "stronger" or "weaker". Thus, it should be understood that a molecule having a higher affinity to FcRn than HSA is considered to bind stronger to FcRn than HSA and a molecule having a lower affinity to FcRn than HSA is considered to bind weaker to FcRn than HSA.

[0074] The terms "longer plasma half-life" or "shorter plasma half-life" and similar expressions are understood to be in relationship to the corresponding parent or reference or corresponding albumin molecule. Thus, a longer plasma half-life with respect to a variant albumin of the invention means that the variant has longer plasma half-life than the corresponding albumin having the same sequences except for the alteration(s) described herein, e.g. at one or more (several) positions in Domain I and one or more (several) positions in Domain III (e.g. in SEQ ID NO: 2).

[0075] Reference: a reference is an albumin, fusion, conjugate, composition, associate or nanoparticle to which an albumin variant, fusion, conjugate, composition, associate or nanoparticle is compared. The reference may comprise or consist of full length albumin (such as HSA or a natural allele thereof) of a fragment thereof. A reference may also be referred to as a 'corresponding' albumin, fusion, conjugate, composition, associate or nanoparticle to which an albumin variant, fusion, conjugate, composition, associate or nanoparticle is compared. A reference may comprise or consist of HSA (SEQ ID NO: 2) or a fragment, fusion, conjugate, associate, nanoparticle or microparticle thereof. Preferably, the reference is identical to the polypeptide, fusion polypeptide, conjugate, composition, associate, nanoparticle or microparticle according to the invention ("being studied") with the exception of the albumin moiety. Preferably the albumin moiety of the reference comprises or consists of an albumin (e.g. HSA, SEQ ID NO: 2) or a fragment thereof. The amino acid sequence of the albumin moiety of the reference may be longer than, shorter than or, preferably, the same (± 1 to 15 amino acids) length as the amino sequence of the albumin moiety of the polypeptide, fusion polypeptide, conjugate, composition, associate, nanoparticle or microparticle according to the invention ("being studied").

[0076] Equivalent amino acid positions: Throughout this specification amino acid positions are defined in relation to full-length mature human serum albumin (i.e. without leader sequence, SEQ ID NO: 2). However, the skilled person understands that the invention also relates to variants of non-human albumins e.g. those disclosed herein) and/or fragments of a human or non-human albumin. Equivalent positions can be identified in fragments of human serum albumin, in animal albumins and in fragments, fusions and other derivative or variants thereof by comparing amino acid sequences using pairwise (e.g. ClustalW) or multiple (e.g. MUSCLE) alignments. For example, Fig. 1 shows that positions equivalent to 500, 550 and 573 in full length human serum albumin are easily identified in fragments of human serum albumin and in albumins of other species. Positions 500, 550 and 573 are indicated by arrows. Further details are provided in the table below.

Example of identification of equivalent positions in HSA, animal albumins and albumin fragments

[0077]

Organism (accession number of protein)	Albumin			Position equivalent to human serum albumin (native amino acid):		
	Full length or fragment	Fragment details	Total length of mature protein	500 (K)	550 (D)	573 (K)
<i>Homo sapiens</i> (AAA98797)	Full length	-	585	500 (K)	550 (D)	573 (K)
<i>Homo sapiens</i>	Fragment	DI, DIII	399	314 (K)	364 (D)	387 (K)
<i>Homo sapiens</i>	Fragment	DI, DIII	403	318 (K)	368 (D)	391 (K)
<i>Macaca mulatta</i> (NP_001182578)	Full length	-	584	500 (K)	550 (N)	573 (P)
<i>Rattus norvegicus</i> (AAH85359)	Full length	-	584	500 (K)	550 (D)	573 (P)
<i>Mus musculus</i> (AAH49971)	Full length	-	584	500 (K)	550 (D)	573 (P)

[0078] Fig. 1 was generated by MUSCLE using the default parameters including output in ClustalW 1.81 format. The raw output data was shaded using BoxShade 3.21 (http://www.ch.embnet.org/software/BOX_form.html) using Output Format: RTF_new; Font Size: 10; Consensus Line: no consensus line; Fraction of sequences (that must agree for shading): 0.5; Input sequence format: ALN. Therefore, throughout this specification amino acid positions defined in human serum albumin also apply to equivalent positions in fragments, derivatives or variants and fusions of human serum albumin, animals from other species and fragments and fusions thereof. Such equivalent positions may have (i) a different residue number in its native protein and/or (ii) a different native amino acid in its native protein.

[0079] Likewise, Fig. 2 shows that equivalent positions can be identified in fragments (e.g. domains) of an albumin with reference to SEQ ID NO: 2 (HSA).

Conventions for Designation of Variants

[0080] For purposes of the present invention, the mature polypeptide disclosed in SEQ ID NO: 2 is used to determine the corresponding amino acid residue in another albumin. The amino acid sequence of another albumin is aligned with the mature polypeptide disclosed in SEQ ID NO: 2, and based on the alignment, the amino acid position number corresponding to any amino acid residue in the mature polypeptide disclosed in SEQ ID NO: 2 is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 3.0.0 or later, more preferably version 5.0.0 or later.

[0081] Identification of the corresponding amino acid residue in another albumin can be determined or confirmed by an alignment of multiple polypeptide sequences using a suitable computer program including, but not limited to, "ClustalW" (Larkin et al., 2007, Bioinformatics 23: 2947-2948), MUSCLE (multiple sequence comparison by log-expectation; version 3.5 or later; Edgar, 2004, Nucleic Acids Research 32: 1792-1797), MAFFT (version 6.857 or later; Katoh and Kuma, 2002, Nucleic Acids Research 30: 3059-3066; Katoh et al., 2005, Nucleic Acids Research 33: 511-518; Katoh and Toh, 2007, Bioinformatics 23: 372-374; Katoh et al., 2009, Methods in Molecular Biology 537: 39-64; Katoh and Toh, 2010, Bioinformatics 26: 1899-1900), and EMBOSS EMMA employing ClustalW (1.83 or later; Thompson et al., 1994, Nucleic Acids Research 22: 4673-4680), using their respective default parameters.

[0082] When the other polypeptide (or protein) has diverged from the mature polypeptide of SEQ ID NO: 2 such that traditional sequence-based comparison fails to detect their relationship (Lindahl and Elofsson, 2000, J. Mol. Biol. 295: 613-615), other pairwise sequence comparison algorithms can be used. Greater sensitivity in sequence-based searching can be attained using search programs that utilize probabilistic representations of polypeptide families (profiles) to search databases. For example, the PSI-BLAST program generates profiles through an iterative database search process and is capable of detecting remote homologs (Atschul et al., 1997, Nucleic Acids Res. 25: 3389-3402). Even greater sensitivity can be achieved if the family or superfamily for the polypeptide has one or more (several) representatives in the protein structure databases. Programs such as GenTHREADER (Jones, 1999, J. Mol. Biol. 287: 797-815; McGuffin and Jones, 2003, Bioinformatics 19: 874-881) utilize information from a variety of sources (PSI-BLAST, secondary structure prediction, structural alignment profiles, and solvation potentials) as input to a neural network that predicts the structural fold for a query sequence. Similarly, the method of Gough et al., 2000, J. Mol. Biol. 313: 903-919, can be used to align

a sequence of unknown structure with the superfamily models present in the SCOP database. These alignments can in turn be used to generate homology models for the polypeptide, and such models can be assessed for accuracy using a variety of tools developed for that purpose. For proteins of known structure, several tools and resources are available for retrieving and generating structural alignments. For example the SCOP superfamilies of proteins have been structurally aligned, and those alignments are accessible and downloadable. Two or more protein structures can be aligned using a variety of algorithms such as the distance alignment matrix (Holm and Sander, 1998, Proteins 33: 88-96) or combinatorial extension (Shindyalov and Bourne, 1998, Protein Engineering 11: 739-747), and implementation of these algorithms can additionally be utilized to query structure databases with a structure of interest in order to discover possible structural homologs (e.g., Holm and Park, 2000, Bioinformatics 16: 566-567).

[0083] In describing the albumin variants of the present invention, the nomenclature described below is adapted for ease of reference. The accepted IUPAC single letter or three letter amino acid abbreviation is employed. The term 'point mutation' and/or 'alteration' includes deletions, insertions and substitutions.

[0084] Substitutions. For an amino acid substitution, the following nomenclature is used: Original amino acid, position, substituted amino acid. Accordingly, for example the substitution of threonine with alanine at position 226 is designated as "Thr226Ala" or "T226A". Multiple mutations (or alterations) are separated by addition marks ("+"), e.g., "Gly205Arg + Ser411Phe" or "G205R + S411F", representing substitutions at positions 205 and 411 of glycine (G) with arginine (R) and serine (S) with phenylalanine (F), respectively. The Figures also use ("/"), e.g., "E492T/N503D" this should be viewed as interchangeable with ("+").

[0085] Deletions. For an amino acid deletion, the following nomenclature is used: Original amino acid, position*. Accordingly, the deletion of glycine at position 195 is designated as "Gly195*" or "G195*". Multiple deletions are separated by addition marks ("+"), e.g., "Gly195* + Ser411*" or "G195* + S411*".

[0086] Insertions. As disclosed above, an insertion may be to the N-side ('upstream', 'X-1') or C-side ('downstream', 'X+1') of the amino acid occupying a position ('the named (or original) amino acid', 'X').

[0087] For an amino acid insertion to the C-side ('downstream', 'X+1') of the original amino acid ('X'), the following nomenclature is used: Original amino acid, position, original amino acid, inserted amino acid. Accordingly the insertion of lysine after glycine at position 195 is designated "Gly195GlyLys" or "G195GK". An insertion of multiple amino acids is designated [Original amino acid, position, original amino acid, inserted amino acid #1, inserted amino acid #2; etc.]. For example, the insertion of lysine and alanine after glycine at position 195 is indicated as "Gly195GlyLysAla" or "G195GKA".

[0088] In such cases the inserted amino acid residue(s) are numbered by the addition of lower case letters to the position number of the amino acid residue preceding the inserted amino acid residue(s). In the above example, the sequence would thus be:

Parent:	Variant:
195	195 195a 195b
G	G - K - A

[0089] For an amino acid insertion to the N-side ('upstream', 'X-1') of the original amino acid (X), the following nomenclature is used: Original amino acid, position, inserted amino acid, original amino acid. Accordingly the insertion of lysine (K) before glycine (G) at position 195 is designated "Gly195LysGly" or "G195KG". An insertion of multiple amino acids is designated [Original amino acid, position, inserted amino acid #1, inserted amino acid #2; etc., original amino acid]. For example, the insertion of lysine (K) and alanine (A) before glycine at position 195 is indicated as "Gly195LysAlaGly" or "G195KAG". In such cases the inserted amino acid residue(s) are numbered by the addition of lower case letters with prime to the position number of the amino acid residue following the inserted amino acid residue(s). In the above example, the sequence would thus be:

Parent:	Variant:
195	195a' 195b' 195
G	K - A - G

[0090] Multiple alterations. Variants comprising multiple alterations are separated by addition marks ("+"), e.g., "Arg170Tyr+Gly195Glu" or "R170Y+G195E" representing a substitution of tyrosine and glutamic acid for arginine and glycine at positions 170 and 195, respectively.

[0091] Different alterations (e.g. substitutions). Where different alterations (e.g. substitutions) can be introduced at a

position, the different alterations (e.g. substitutions) are separated by a comma, e.g., "Arg 170Tyr,Glu" represents a substitution of arginine with tyrosine or glutamic acid at position 170. Thus, "Tyr167Gly,Ala + Arg170Gly,Ala" designates the following variants: "Tyr167Gly+Arg170Gly", "Tyr167Gly+Arg170Ala", "Tyr167Ala+Arg170Gly", and "Tyr167Ala+Arg170Ala".

Detailed Description of the Invention

[0092] The present invention relates to albumin variants, comprising an alteration at position in Domain I and an alteration at a position in Domain III of the mature polypeptide of SEQ ID NO: 2, or at equivalent positions in other albumins or fragments thereof.

Variants

[0093] A first aspect of the invention provides polypeptides which are variant albumins or fragments thereof, or fusion polypeptides comprising the variant albumin or fragment thereof, of a parent albumin, comprising one or more (several) alterations in Domain I of albumin, such as HSA (SEQ ID NO: 2) and one or more (several) alterations in Domain III of albumin, such as HSA (SEQ ID NO: 2).

[0094] It is preferred that the parent albumin and/or the variant albumin comprises or consists of:

- (a) a polypeptide having at least 60% sequence identity to the mature polypeptide of SEQ ID NO: 2;
- (b) a polypeptide encoded by a polynucleotide that hybridizes under low stringency conditions with (i) the mature polypeptide coding sequence of SEQ ID NO: 1, or (ii) the full-length complement of (i);
- (c) a polypeptide encoded by a polynucleotide having at least 60% identity to the mature polypeptide coding sequence of SEQ ID NO: 1; and/or
- (d) a fragment of the mature polypeptide of SEQ ID NO: 2.

[0095] The variants of albumin or fragments thereof or fusion polypeptides comprising albumin or fragments thereof comprise one or more (several) alterations, such as substitutions, deletions or insertions at positions in Domain I and one or more (several) alterations, such as substitutions, deletions or insertions at positions in Domain III of the mature polypeptide of SEQ ID NO: 2 or in equivalent positions of other albumins or variants or fragments thereof. A stop codon may be introduced in addition to the alterations described herein and if introduced is at position 574 or further downstream (e.g. in SEQ ID NO: 2 it is introduced at from position 574 to 585).

[0096] The variant albumin, a fragment thereof, or albumin part of a fusion polypeptide comprising variant albumin or a fragment thereof according to the invention has generally a sequence identity to the sequence of HSA shown in SEQ ID NO: 2 of at least 60%, preferably at least 70%, preferably at least 80%, preferably at least 85%, preferably at least 90 %, more preferred at least 95%, more preferred at least 96%, more preferred at least 97%, more preferred at least 98% and most preferred at least 99%. The variant has less than 100% identity to SEQ ID NO: 2.

[0097] The variant albumin, a fragment thereof, or albumin part of a fusion polypeptide comprising variant albumin or a fragment thereof according to the invention has generally a sequence identity to the sequence of the parent albumin of at least 60%, preferably at least 70%, preferably at least 80%, preferably at least 85%, preferably at least 90 %, more preferred at least 95%, more preferred at least 96%, more preferred at least 97%, more preferred at least 98% and most preferred at least 99%. The variant has less than 100% identity to the sequence of the parent albumin.

[0098] In one aspect, the number of alterations in the variants of the invention is 1 to 20, e.g., 1 to 10 and 1 to 5, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 alterations relative to SEQ ID NO: 2 or relative to the sequence of the parent albumin.

[0099] The one or more (several) alterations in Domain I may be selected from positions corresponding to positions from 78 to 88 (i.e. 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88) and/or from 105 to 120 (i.e. 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120) of HSA (SEQ ID NO: 2). In HSA positions 78 to 88 form a loop and positions 105 to 120 form a loop. Therefore, positions in equivalent loops of other albumins are also included in the invention. Preferred residues are residues 81 to 85, particularly 82 and 83, and residues 110 to 114, particularly 111 and 112.

[0100] At position 82 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to Q, D or A, even more preferred to D or A and most preferred to A. In SEQ ID NO: 2 the native amino acid at position 82 is glutamic acid, therefore a substitution to glutamic acid is not preferred.

[0101] At position 83 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, K or S, even more preferred to N or K and most preferred to N. In SEQ ID NO: 2 the native amino acid at position 83 is threonine, therefore a substitution to threonine is not preferred.

[0102] At position 111 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, E, Q, D, G or H, even more preferred to E or Q and most preferred to E. In SEQ ID NO: 2 the native amino acid at position 111 is asparagine, therefore a substitution to asparagine is not preferred.

[0103] At position 112 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to F, Y or W, even more preferred to F or Y and most preferred to F. In SEQ ID NO: 2 the native amino acid at position 112 is leucine, therefore a substitution to leucine is not preferred.

[0104] At position 573 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to P, Y, W, H, F, T, I or V, even more preferred to P, Y or W and most preferred to P. In SEQ ID NO: 2 the native amino acid at position 573 is lysine, therefore a substitution to lysine is not preferred.

[0105] An albumin variant may comprise alterations, e.g. substitutions, at positions 82 and 83; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0106] An albumin variant may comprise alterations, e.g. substitutions, at positions 82 and 111; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0107] An albumin variant may comprise alterations, e.g. substitutions, at positions 82 and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0108] An albumin variant may comprise alterations, e.g. substitutions, at positions 82 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0109] An albumin variant may comprise alterations, e.g. substitutions, at positions 83 and 111; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0110] An albumin variant may comprise alterations, e.g. substitutions, at positions 83 and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0111] An albumin variant may comprise alterations, e.g. substitutions, at positions 83 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0112] An albumin variant may comprise alterations, e.g. substitutions, at positions 111 and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0113] An albumin variant may comprise alterations, e.g. substitutions, at positions 111 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0114] An albumin variant may comprise alterations, e.g. substitutions, at positions 112 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0115] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, and 111; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0116] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0117] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0118] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 111, and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0119] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 111, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0120] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 112, and 573; of SEQ ID NO:

2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0121] An albumin variant may comprise alterations, e.g. substitutions, at positions 83, 111, and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0122] An albumin variant may comprise alterations, e.g. substitutions, at positions 83, 111, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0123] An albumin variant may comprise alterations, e.g. substitutions, at positions 83, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0124] An albumin variant may comprise alterations, e.g. substitutions, at positions 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0125] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, 111, and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0126] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, 111, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0127] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0128] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0129] An albumin variant may comprise alterations, e.g. substitutions, at positions 83, 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0130] An albumin variant may comprise alterations, e.g. substitutions, at positions 82, 83, 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0131] An albumin variant may comprise alterations, e.g. substitutions, at positions 425 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0132] An albumin variant may comprise alterations, e.g. substitutions, at positions 505 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0133] An albumin variant may comprise alterations, e.g. substitutions, at positions 527 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0134] An albumin variant may comprise alterations, e.g. substitutions, at positions 534 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0135] Particularly preferred albumin variants comprise substitutions T83N/N111E (e.g. SEQ ID NO: 32); T83N/N111E/K573P (e.g. SEQ ID NO: 33); T83N/K573P (e.g. SEQ ID NO: 34); T83K/K573P (e.g. SEQ ID NO: 38); E82A/K573P (e.g. SEQ ID NO: 39); L112F/K573P (e.g. SEQ ID NO: 40); E82D/K573P (e.g. SEQ ID NO: 43); P110G/K573P (e.g. SEQ ID NO: 44); N111D/K573P (e.g. SEQ ID NO: 60); N111G/K573P (e.g. SEQ ID NO: 61); N111H/K573P (e.g. SEQ ID NO: 62); E425A/K573P (e.g. SEQ ID NO: 64); E505Q/K573P (e.g. SEQ ID NO: 65); T527M/K573P (e.g. SEQ ID NO: 66); N111E/K573P (e.g. SEQ ID NO: 68); K534V/K573P (e.g. SEQ ID NO: 73); N111Q/K573P (e.g. SEQ ID NO: 74) which are described with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0136] Also, an albumin variant according to the invention may comprise one or more (several) alterations at positions selected from 78 to 88 (78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91) and/or 105 to 120 (105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120) and/or 425, 505, 510, 512, 524, 527, 531, 534, 569, 575 of HSA (SEQ ID NO: 2) or equivalent positions of other albumins. Preferred alterations are substitutions such as those described for these positions in the first aspect of the invention. Particularly preferred substitutions include D108A (SEQ ID NO: 59); D108E (e.g. SEQ ID NO: 70); N109K (e.g. SEQ ID NO: 69); P110G (e.g. SEQ ID NO: 42); N111D (e.g. SEQ

ID NO: 46); N111E (e.g. SEQ ID NO: 67); N111G (e.g. SEQ ID NO: 48); N111H (e.g. SEQ ID NO: 49); N111K (e.g. SEQ ID NO: 54); L112F (e.g. SEQ ID NO: 37); E425A (e.g. SEQ ID NO: 63); E425K (e.g. SEQ ID NO: 55); E505Q (e.g. SEQ ID NO: 45); H510D (e.g. SEQ ID NO: 57); D512E (e.g. SEQ ID NO: 50); K524A (e.g. SEQ ID NO: 51); T527A (e.g. SEQ ID NO: 52); T527M (e.g. SEQ ID NO: 47); E531H (e.g. SEQ ID NO: 53); K534V (e.g. SEQ ID NO: 56); A569S (e.g. SEQ ID NO: 58); L575F (e.g. SEQ ID NO: 72); E82A (e.g. SEQ ID NO: 36); E82D (e.g. SEQ ID NO: 41); T83K (e.g. SEQ ID NO: 35); T83N (e.g. SEQ ID NO: 71) which are described with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprising one or more (several) alterations may comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0137] It is preferred that the variant albumin, a fragment thereof or fusion polypeptide comprising the variant albumin or fragment thereof has altered binding affinity to FcRn and/or an altered plasma half-life compared with the corresponding parent or reference albumin, fragment thereof, or fusion polypeptide comprising the variant albumin or fragment thereof and/or an altered binding affinity to FcRn.

[0138] In a particularly preferred embodiment the parent or reference albumin is HSA (SEQ ID NO: 2) and the variant albumin, a fragment thereof or fusion polypeptide comprising the variant albumin or fragment thereof has altered binding affinity to FcRn and/or an altered plasma half-life compared with the HSA, the corresponding fragment or fusion polypeptide comprising HSA or fragment thereof and/or an altered binding affinity to FcRn.

[0139] The correlation between binding of albumin to its receptor and plasma half-life has been realized by the present inventors based on the natural occurring allele of HSA D494N. The inventors have previously analyzed this allele and found that it has a lower affinity to its receptor FcRn than the affinity of WT HSA to FcRn.

[0140] Further, it has been disclosed that a transgenic mouse having the natural mouse FcRn replaced with human FcRn has a higher serum albumin level than normal mouse (J Exp Med. (2003) 197(3):315-22). The inventors have previously discovered that human FcRn has a higher affinity to mouse serum albumin than mouse FcRn has to mouse serum albumin and, therefore, the observed increase in serum albumin in the transgenic mice corresponds with a higher affinity between serum albumin and its receptor, confirming the correlation between albumin binding to FcRn and plasma half-life. In addition, variants of albumin that have little or no binding to FcRn have been shown to have reduced half-life in a mouse model, Kenanova et al (2009) J. Nucl. Med.; 50 (Supplement 2):1582).

[0141] One way to determine whether the affinity of a variant albumin to FcRn is higher or lower than the parent or reference albumin is to use the Surface Plasmon Resonance assay (SPR) as described below. The skilled person will understand that other methods might be useful to determine whether the affinity of a variant albumin to FcRn is higher or lower than the affinity of the parent or reference albumin to FcRn, e.g., determination and comparison of the binding constants KD. The binding affinity (KD) between a first molecule (e.g. ligand) and a second molecule (e.g. receptor) is a function of the kinetic constants for association (on rate, k_a) and dissociation (off-rate, k_d) according to $KD = k_d/k_a$. Thus, according to the invention variant albumins having a KD that is lower than the KD for natural HSA is considered to have a higher plasma half-life than HSA and variant albumins having a KD that is higher than the KD for natural HSA is considered to have a lower plasma half-life than HSA.

[0142] In an embodiment of the invention, the variants of albumin or fragments thereof, or fusion polypeptides comprising variant albumin or a fragment thereof according to the invention have a plasma half-life that is longer than the plasma half-life of the parent or reference albumin fragment thereof or fusion polypeptide comprising the parent or reference albumin or a fragment thereof and/or an stronger binding affinity to FcRn.

[0143] In a further embodiment the variants of albumin or fragments thereof, or fusion polypeptides comprising variant albumin or fragments thereof according to the invention have a plasma half-life that is shorter than the plasma half-life of the parent or reference albumin fragment thereof or fusion polypeptide comprising the parent or reference albumin or a fragment thereof and/or an weaker binding affinity to FcRn.

[0144] In addition to alterations at positions in Domains I (such as within loop 78 to 88 and/or within loop 105 to 120 as described herein) and III (or equivalent position of other albumins or variants of fragments thereof) the variant albumin or fragments thereof, or fusion polypeptides comprising variant albumin or fragments thereof according to the invention may contain additional substitutions, deletions or insertions in other positions of the molecules. Such additional substitutions, deletions or insertions may be useful in order to alter other properties of the molecules such as but not limited to altered glycosylation; introduction of reactive groups of the surface such a thiol groups, removing/generating a carbamoylation site; etc.

[0145] Residues that might be altered in order to provide reactive residues on the surface and which advantageously could be applied to the invention has been disclosed in WO2010/092135 (incorporated herein by reference). Particular preferred residues include the positions corresponding to positions in SEQ ID NO: 2.

[0146] As examples of alterations that can be made in SEQ ID NO: 2 or in corresponding positions in other albumins in order to provide a reactive thiol group on the surface includes alterations corresponding to following alterations in SEQ ID NO: 2: L585C, D1C, A2C, D562C, A364C, A504C, E505C, T79C, E86C, D129C, D549C, A581C, D121C, E82C, S270C, A578C, L595LC, D1DC, A2AC, D562DC, A364AC, A504AC, E505EC, T79TC, E86EC, D129DC, D549DC, A581AC, A581AC, D121DC, E82EC, S270SC, S579AC, C360*, C316*, C75*, C168*, C558*, C361*, C91*, C124*,

C169* and C567*. Alternatively a cysteine residue may be added to the N or C terminal of albumin. The term 'reactive thiol' means and/or includes a thiol group provided by a Cys which is not disulphide bonded to a Cysteine and/or which is sterically available for binding to a partner such as a conjugation partner.

5 Fusion polypeptides

[0147] A second aspect of the invention relates to fusion polypeptides. Therefore, the variants of albumin or fragments thereof according to the invention may be fused with a non-albumin polypeptide fusion partner. The fusion partner may in principle be any polypeptide but generally it is preferred that the fusion partner is a polypeptide having therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial properties. Such properties may be referred to as 'pharmaceutically beneficial properties'. Fusion polypeptides comprising albumin or fragments thereof are known in the art. It has been found that such fusion polypeptides comprising albumin or a fragment thereof and a fusion partner polypeptide have a longer plasma half-life compared to the unfused fusion partner polypeptide alone. According to the invention it is possible to alter the plasma half-life of the fusion polypeptides according to the invention compared to the corresponding fusion polypeptides of the prior art. 'Alter' includes both increasing the plasma half-life and decreasing the plasma half-life. Increasing the plasma half-life is preferred. The invention allows tailoring of half-life to a term desired.

[0148] One or more (several) therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial may be fused to the N-terminus, the C-terminus of albumin, inserted into a loop in the albumin structure or any combination thereof. It may or it may not comprise linker sequences separating the various components of the fusion polypeptide.

[0149] Teachings relating to fusions of albumin or a fragment thereof are known in the art and the skilled person will appreciate that such teachings can also be applied to the invention. WO 2001/79271A (particularly page 9 and/or Table 1), WO 2003/59934 (particularly Table 1), WO03/060071 (particularly Table 1) and WO01/079480 (particularly Table 1) (each incorporated herein by reference in their entirety) also contain examples of therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial polypeptides that may be fused to albumin or fragments thereof, and these examples apply also to the invention.

[0150] Further preferences for the second aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

30 Polynucleotides

[0151] A third aspect of the invention relates to isolated polynucleotides that encode any of the variants or fusion polypeptides of the invention. The polynucleotide may be an isolated polynucleotide. The polynucleotide may be comprised a in a vector (such as a plasmid) and/or in a host cell.

[0152] Further preferences for the third aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

40 Nucleic Acid Constructs

[0153] A fourth aspect of the invention relates to nucleic acid constructs comprising a polynucleotide encoding a variant or fusion polypeptide of the invention operably linked to one or more (several) control sequences that direct the expression of the coding sequence in a suitable host cell under conditions compatible with the control sequences.

[0154] A polynucleotide may be manipulated in a variety of ways to provide for expression of a variant. Manipulation of the polynucleotide prior to its insertion into a vector may be desirable or necessary depending on the expression vector. The techniques for modifying polynucleotides utilizing recombinant DNA methods are well known in the art.

[0155] The control sequence may be a promoter sequence, which is recognized by a host cell for expression of the polynucleotide. The promoter sequence contains transcriptional control sequences that mediate the expression of the variant. The promoter may be any nucleic acid sequence that shows transcriptional activity in the host cell including mutant, truncated, and hybrid promoters, and may be obtained from genes encoding extracellular or intracellular polypeptides either homologous or heterologous to the host cell.

[0156] In a yeast host, useful promoters are obtained from the genes for *Saccharomyces cerevisiae* enolase (ENO-1), *Saccharomyces cerevisiae* protease A (PRA1), *Saccharomyces cerevisiae* protease B (PRB1), *Saccharomyces cerevisiae* translation elongation factor (TEF1), *Saccharomyces cerevisiae* translation elongation factor (TEF2), *Saccharomyces cerevisiae* galactokinase (GAL1), *Saccharomyces cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH1, ADH2/GAP), *Saccharomyces cerevisiae* triose phosphate isomerase (TPI), *Saccha-*

Saccharomyces cerevisiae metallothionein (CUP1), and *Saccharomyces cerevisiae* 3-phosphoglycerate kinase. Other useful promoters for yeast host cells are described by Romanos et al., 1992, Yeast 8: 423-488.

[0157] The skilled person knows useful promoters for use in rice and mammalian cells, such as CHO or HEK. In a rice host, useful promoters are obtained from cauliflower mosaic virus 35S RNA gene (CaMV35S), maize alcohol dehydrogenase (Adh1) and alpha Amy3.

[0158] In a mammalian host cell, such as CHO or HEK, useful promoters are obtained from Cytomegalovirus (CMV) and CAG hybrid promoter (hybrid of CMV early enhancer element and chicken beta-actin promoter), Simian vacuolating virus 40 (SV40).

[0159] The control sequence may also be a suitable transcription terminator sequence, which is recognized by a host cell to terminate transcription. The terminator sequence is operably linked to the 3'-terminus of the polynucleotide encoding the variant. Any terminator that is functional in the host cell may be used.

[0160] Preferred terminators for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* enolase, *Saccharomyces cerevisiae* cytochrome C (CYC1), *Saccharomyces cerevisiae* alcohol dehydrogenase (ADH1) and *Saccharomyces cerevisiae* glyceraldehyde-3-phosphate dehydrogenase. Other useful terminators for yeast host cells are described by Romanos et al., 1992, supra. The skilled person knows useful terminators for use in rice and mammalian cells, such as CHO or HEK. For example, in a rice host, preferred terminators are obtained from Agrobacterium tumefaciens nopaline synthase (Nos) and cauliflower mosaic virus 35S RNA gene (CaMV35S).

[0161] The control sequence may also be a suitable leader sequence, a nontranslated region of an mRNA that is important for translation by the host cell. The leader sequence is operably linked to the 5'-terminus of the polynucleotide encoding the variant. Any leader sequence that is functional in the host cell may be used.

[0162] Suitable leaders for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* enolase (ENO-1), *Saccharomyces cerevisiae* 3-phosphoglycerate kinase, *Saccharomyces cerevisiae* alpha-factor, and *Saccharomyces cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH2/GAP).

[0163] The control sequence may also be a polyadenylation sequence, a sequence operably linked to the 3'-terminus of the variant-encoding sequence and, when transcribed, is recognized by the host cell as a signal to add polyadenosine residues to transcribed mRNA. Any polyadenylation sequence that is functional in the host cell may be used.

[0164] Useful polyadenylation sequences for yeast host cells are described by Guo and Sherman, 1995, Mol. Cellular Biol. 15: 5983-5990.

[0165] The control sequence may also be a signal peptide coding region that encodes a signal peptide linked to the N-terminus of a variant and directs the variant into the cell's secretory pathway. The 5'-end of the coding sequence of the polynucleotide may inherently contain a signal peptide coding region naturally linked in translation reading frame with the segment of the coding region that encodes the variant. Alternatively, the 5'-end of the coding sequence may contain a signal peptide coding region that is foreign to the coding sequence. The foreign signal peptide coding region may be required where the coding sequence does not naturally contain a signal peptide coding region. Alternatively, the foreign signal peptide coding region may simply replace the natural signal peptide coding region in order to enhance secretion of the variant. However, any signal peptide coding region that directs the expressed variant into the secretory pathway of a host cell may be used.

[0166] Useful signal peptides for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* alpha-factor and *Saccharomyces cerevisiae* invertase. Other useful signal peptide coding sequences are described by Romanos et al., 1992, supra. The skilled person knows useful signal peptides for use in rice and mammalian cells, such as CHO or HEK.

[0167] Where both signal peptide and propeptide regions are present at the N-terminus of a variant, the propeptide region is positioned next to the N-terminus of the variant and the signal peptide region is positioned next to the N-terminus of the propeptide region.

[0168] Further preferences for the fourth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Preparation of Variants

[0169] A fifth aspect of the invention relates to a method for preparing or obtaining a variant albumin or fragment thereof, or fusion polypeptides comprising the variant albumin or fragments thereof, or associates of variant albumin or fragment thereof comprising:

- (a) introducing into a parent albumin or fragments thereof, or fusion polypeptides comprising the parent albumin or fragments thereof one or more (several) alterations in Domain I and one or more (several) alterations in Domain III; and
- (b) recovering the variant albumin or fragment thereof, or fusion polypeptides comprising the variant albumin or

fragment thereof.

[0170] Preferred alterations are as described in relation to the first aspect of the invention. The resultant variant albumin or fragment thereof may have altered FcRn-binding affinity compared to the FcRn-binding affinity of a reference such as a parent albumin or fragment which does not comprise the alterations. More preferably, the resultant variant albumin or fragment thereof has a stronger FcRn-binding affinity.

[0171] The invention includes a method for preparing a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof having a binding affinity to FcRn which is altered compared to the binding affinity of a reference albumin, fragment or fusion thereof to FcRn, comprising:

(a) providing a nucleic acid encoding a parent albumin such as an albumin having at least 60% sequence identity to SEQ ID NO: 2;

(b) modifying the sequence of step (a), to encode a polypeptide which is a variant albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof comprising:

(i) alterations at positions corresponding to one or more (several) positions in Domain I of the parent albumin and one or more (several) positions in Domain III (Domain 3), or

(ii) alterations at positions corresponding to one or more (several) of any of positions 78 to 120 of Domain I of SEQ ID NO: 2 or at positions corresponding to one or more (several) of any of positions 425, 505, 510, 512, 524, 527, 531, 534, 569, 573, 575 of Domain III of SEQ ID NO: 2;

(c) optionally, introducing the modified sequence of step (b) in a suitable host cell;

(d) optionally, growing the cells in a suitable growth medium under condition leading to expression of the polypeptide; and

(e) optionally, recovering the polypeptide from the growth medium;

wherein the polypeptide has an altered binding affinity to FcRn and/or an altered plasma half-life compared with the half-life of a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof.

[0172] It is preferred that the parent albumin and/or the variant albumin comprises or consists of:

(a) a polypeptide having at least 60% sequence identity to the mature polypeptide of SEQ ID NO: 2;

(b) a polypeptide encoded by a polynucleotide that hybridizes under low stringency conditions with (i) the mature polypeptide coding sequence of SEQ ID NO: 1, or (ii) the full-length complement of (i);

(c) a polypeptide encoded by a polynucleotide having at least 60% identity to the mature polypeptide coding sequence of SEQ ID NO: 1; and/or

(d) a fragment of the mature polypeptide of SEQ ID NO: 2.

[0173] The variants can be prepared by those skilled persons using any mutagenesis procedure known in the art, such as site-directed mutagenesis, synthetic gene construction, semi-synthetic gene construction, random mutagenesis, shuffling, etc.

[0174] Site-directed mutagenesis is a technique in which one or more (several) mutations (alterations) are created at one or more (several) defined sites in a polynucleotide encoding the parent.

[0175] Site-directed mutagenesis can be accomplished *in vitro* by PCR involving the use of oligonucleotide primers containing the desired mutation. Site-directed mutagenesis can also be performed *in vitro* by cassette mutagenesis involving the cleavage by a restriction enzyme at a site in the plasmid comprising a polynucleotide encoding the parent and subsequent ligation of an oligonucleotide containing the mutation in the polynucleotide. Usually the restriction enzyme that digests at the plasmid and the oligonucleotide is the same, permitting ligation of the plasmid and insert to one another. See, e.g., Scherer and Davis, 1979, Proc. Natl. Acad. Sci. USA 76: 4949-4955; and Barton et al., 1990, Nucleic Acids Res. 18: 7349-4966.

[0176] Site-directed mutagenesis can also be accomplished *in vivo* by methods known in the art. See, e.g., U.S. Patent Application Publication NO: 2004/0171154; Storici et al., 2001, Nature Biotechnol. 19: 773-776; Kren et al., 1998, Nat. Med. 4: 285-290; and Calissano and Macino, 1996, Fungal Genet. Newslett. 43: 15-16.

[0177] Any site-directed mutagenesis procedure can be used in the invention. There are many commercial kits available that can be used to prepare variants.

[0178] Synthetic gene construction entails *in vitro* synthesis of a designed polynucleotide molecule to encode a polypeptide of interest. Gene synthesis can be performed utilizing a number of techniques, such as the multiplex microchip-based technology described by Tian et al. (2004, Nature 432: 1050-1054) and similar technologies wherein oligonucle-

otides are synthesized and assembled upon photo-programmable microfluidic chips.

[0179] Single or multiple amino acid substitutions, deletions, and/or insertions can be made and tested using known methods of mutagenesis, recombination, and/or shuffling, followed by a relevant screening procedure, such as those disclosed by Reidhaar-Olson and Sauer, 1988, Science 241: 53-57; Bowie and Sauer, 1989, Proc. Natl. Acad. Sci. USA 86: 2152-2156; WO 95/17413; or WO 95/22625. Other methods that can be used include error-prone PCR, phage display (e.g., Lowman et al., 1991, Biochemistry 30: 10832-10837; U.S. Patent NO: 5,223,409; WO 92/06204) and region-directed mutagenesis (Derbyshire et al., 1986, Gene 46: 145; Ner et al., 1988, DNA 7: 127).

[0180] Mutagenesis/shuffling methods can be combined with high-throughput, automated screening methods to detect activity of cloned, mutagenized polypeptides expressed by host cells (Ness et al., 1999, Nature Biotechnology 17: 893-896). Mutagenized DNA molecules that encode active polypeptides can be recovered from the host cells and rapidly sequenced using standard methods in the art. These methods allow the rapid determination of the importance of individual amino acid residues in a polypeptide.

[0181] Semi-synthetic gene construction is accomplished by combining aspects of synthetic gene construction, and/or site-directed mutagenesis, and/or random mutagenesis, and/or shuffling. Semi-synthetic construction is typified by a process utilizing polynucleotide fragments that are synthesized, in combination with PCR techniques. Defined regions of genes may thus be synthesized *de novo*, while other regions may be amplified using site-specific mutagenic primers, while yet other regions may be subjected to error-prone PCR or non-error prone PCR amplification. Polynucleotide sub sequences may then be shuffled.

[0182] Further preferences for the fifth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Methods of Production

[0183] A sixth aspect of the invention relates to methods of preparation of a variant according to the invention. The variants of the invention can be prepared using techniques well known to the skilled person. One convenient way is by cloning nucleic acid encoding the parent albumin or a fragment thereof or fusion polypeptide comprising albumin or a fragment thereof, modifying said nucleic acid to introduce the desired substitution(s) at positions in Domain I and Domain III of the mature polypeptide of SEQ ID NO: 2 (or equivalent positions in other albumins or fragments thereof), preparing a suitable genetic construct where the modified nucleic acid is placed in operative connection with suitable regulatory genetic elements, such as promoter, terminator, activation sites, ribosome binding sites etc., introducing the genetic construct into a suitable host organism, culturing the transformed host organism under conditions leading to expression of the variant and recovering the variant. All these techniques are known in the art and it is within the skills of the average practitioner to design a suitable method for preparing a particular variant according to the invention.

[0184] The variant polypeptide of the invention may also be connected to a signal sequence in order to have the variant polypeptide secreted into the growth medium during culturing of the transformed host organism. It is generally advantageous to have the variant polypeptide secreted into the growth medium in order to ease recovery and purification.

[0185] Techniques for preparing variant polypeptides have also been disclosed in WO 2009019314 (included by reference) and these techniques may also be applied to the invention.

[0186] Albumins have been successfully expressed as recombinant proteins in a range of hosts including fungi (including but not limited to *Aspergillus* (WO06066595), *Kluyveromyces* (Fleer 1991, Bio/technology 9, 968-975), *Pichia* (Kobayashi 1998 Therapeutic Apheresis 2, 257-262) and *Saccharomyces* (Sleep 1990, Bio/technology 8, 42-46)), bacteria (Pandjaitab 2000, J. Allergy Clin. Immunol. 105, 279-285)), animals (Barash 1993, Transgenic Research 2, 266-276) and plants (including but not limited to potato and tobacco (Sijmons 1990, Bio/technology 8, 217 and Farran 2002, Transgenic Research 11, 337-346) and rice e.g. *Oryza sativa*) and mammalian cells such as CHO and HEK. The variant polypeptide of the invention is preferably produced recombinantly in a suitable host cell. In principle any host cell capable of producing a polypeptide in suitable amounts may be used and it is within the skills of the average practitioner to select a suitable host cell according to the invention. A preferred host organism is yeast, preferably selected among *Saccharomycaceae*, more preferred *Saccharomyces cerevisiae*.

[0187] The variant polypeptides of the invention may be recovered and purified from the growth medium using a combination of known separation techniques such as filtration, centrifugation, chromatography, and affinity separation techniques etc. It is within the skills of the average practitioner to purify the variants of the invention using a particular combination of such known separation steps. As an example of purification techniques that may be applied to the variants of the invention can be mentioned the teaching of WO00/44772.

[0188] The variant polypeptides of the invention may be used for delivering a therapeutically beneficial compound (including prophylactically beneficial compound such as a vaccine) to an animal or a human individual in need thereof. Such therapeutically beneficial compounds include, but are not limited, to labels and readily detectable compounds for

use in diagnostics, such as various imaging techniques; pharmaceutical active compounds such as drugs, or specifically binding moieties such as antibodies. The variants of the invention may even be connected to two or more (several) different therapeutically beneficial compounds, e.g., an antibody and a drug, which gives the combined molecule the ability to bind specifically to a desired target and thereby provide a high concentration of the connected drug at that particular target.

[0189] Further preferences for the sixth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Conjugates

[0190] A seventh aspect of the invention relates to conjugates (conjugations). Therefore, the variants of albumin or fragments thereof or fusion polypeptides according to the invention may be conjugated to a second molecule ('conjugation partner') using techniques known within the art. The conjugation partner may be a therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial moiety. Said conjugation partner may be a polypeptide or a non-polypeptide chemical. The conjugation partner may be a polypeptide, a chemical (e.g. chemically synthesized drug) or a nucleic acid (e.g. DNA, RNA, siRNA).

[0191] Said second molecule may comprise a diagnostic or imaging moiety, and in this embodiment the conjugate may be useful as a diagnostic tool such as in imaging; or the second molecule may be a therapeutic or prophylactic (e.g. vaccine) compound and in this embodiment the conjugate may be used for therapeutic or prophylactic (e.g. vaccination) purposes where the conjugate will have the therapeutic or prophylactic properties of the therapeutic or prophylactic compound as well as the desirable plasma half-life provided by the albumin part of the conjugate. Conjugates of albumin and a therapeutic molecule are known in the art and it has been verified that such conjugates have long plasma half-life compared with the nonconjugated, free therapeutic molecule as such. According to the invention it is possible to alter the binding affinity to FcRn and/or plasma half-life of the conjugate according to the invention compared to the corresponding conjugates of the prior art. 'Alter' includes both increasing the plasma half-life and decreasing the plasma half-life binding affinity to FcRn and/or increasing the binding affinity and decreasing the binding affinity to FcRn. Increasing the plasma half-life and/or binding affinity to FcRn is preferred. The conjugates may conveniently be linked *via* a free thiol group present on the surface of HSA (amino acid residue 34 of mature HSA) using well known chemistry.

[0192] In one particular preferred aspect the variant albumin or fragment thereof is conjugated to a beneficial therapeutic or prophylactic (including vaccine) compound and the conjugate is used for treatment of a condition in a patient in need thereof, which condition is responsive to the particular selected therapeutic compound. Techniques for conjugating such a therapeutically useful compound to the variant albumin or fragment thereof are known in the art. WO 2009/019314 (incorporated herein by reference in its entirety) discloses examples of techniques suitable for conjugating a therapeutically compound to a polypeptide which techniques can also be applied to the invention. Further WO 2009/019314 discloses examples of compounds and moieties that may be conjugated to substituted transferrin and these examples may also be applied to the invention. The teaching of WO 2009/019314 is included herein by reference.

[0193] HSA contains in its natural form one free thiol group (at Cys34) that conveniently may be used for conjugation. As a particular embodiment within this aspect the variant albumin or fragment thereof may comprise further modifications provided to generate additional free thiol groups on the surface. This has the benefit that the payload of the variant albumin or fragment thereof is increased so that more than one molecule of the therapeutic (e.g. prophylactic) compound can be conjugated to each molecule of variant albumin or fragment thereof, or two or more (several) different therapeutic compounds may be conjugated to each molecule of variant albumin or fragment thereof, e.g., a compound having targeting properties such as an antibody specific for example a tumor; and a cytotoxic drug conjugated to the variant albumin or fragment thereof thereby creating a highly specific drug against a tumor. Teaching of particular residues that may be modified to provide for further free thiol groups on the surface can be found in copending patent application WO 2010/092135, which is incorporated by reference.

[0194] The conjugation partner may alternatively be conjugated to a fusion polypeptide (described herein), resulting in a molecule comprising a fusion partner fused to the albumin as well as a conjugation partner conjugated to the same albumin or even to the fusion partner.

[0195] Further preferences for the seventh aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Associates

[0196] An eighth aspect of the invention relates to associates. Therefore, the variants of albumin or fragments thereof or fusion polypeptides may further be used in form of "associates". In this connection the term "associate" is intended to mean a compound comprising a variant of albumin or a fragment thereof and another compound bound or associated to the variant albumin or fragment thereof by non-covalent binding. As an example of such an associate can be mentioned an associate consisting variant albumin and a lipid associated to albumin by a hydrophobic interaction. Such associates are known in the art and they may be prepared using well known techniques. As an example of a preferred associate according to the invention, can be mentioned an associate comprising variant albumin and a taxane, a taxol or taxol derivative (e.g. paclitaxel). Further examples of associates comprise a therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial moiety.

[0197] The half-life of an albumin associate according to the invention may be longer or shorter than the half-life of the 'other compound' alone. The half-life of an albumin associate according to the invention may be longer or shorter than the half-life of the analogous / equivalent albumin associate comprising or consisting of a reference albumin such as native HSA (instead of an albumin variant or derivative according to the invention) and the 'other compound'. Likewise, the binding affinity to FcRn an albumin associate according to the invention may be stronger or weaker than the binding affinity to FcRn of the analogous / equivalent albumin associate comprising or consisting of a reference albumin such as native HSA (instead of an albumin variant or derivative according to the invention) and the 'other compound'. Methods for the preparation of associates are well-known to the skilled person, for example, formulation (by association) of HSA with Lipo-compounds is described in Hussain, R. and Siligardi, G. (2006) International Journal of Peptide Research and Therapeutics, Vol. 12, NO: 3, pp. 311-315.

[0198] Further preferences for the eighth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Compositions

[0199] A ninth aspect of the invention relates to compositions. Therefore the invention is also directed to the use of a variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, or a conjugate comprising a variant of albumin or a fragment thereof, or an associate comprising a variant of albumin or a fragment thereof for the manufacture of a pharmaceutical composition, wherein the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, or a conjugate comprising a variant of albumin or a fragment thereof, or an associate comprising a variant of albumin or a fragment thereof has an altered binding affinity to FcRn and/or an altered plasma half-life compared with HSA or the corresponding fragment thereof or fusion polypeptide comprising HSA or fragment thereof or conjugate comprising HSA.

[0200] In this connection the corresponding fragment of HSA is intended to mean a fragment of HSA that aligns with and has same number of amino acids as the fragment of the variant albumin with which it is compared. Similarly the corresponding fusion polypeptide comprising HSA or conjugate comprising HSA is intended to mean molecules having same size and amino acid sequence as the fusion polypeptide of conjugate comprising variant albumin, with which it is compared.

[0201] The composition may comprise a pharmaceutically acceptable carrier or excipient such as water, polysorbate 80 or those specified in the US Pharmacopoeia for human albumin.

[0202] Further preferences for the ninth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Nanoparticles

[0203] A tenth aspect of the invention relates to a nanoparticle comprising a variant, fusion, conjugate, associate, nanoparticle, composition or polynucleotide as disclosed herein.

[0204] Techniques for incorporation of a molecule into nano- or microparticles are known in the art. Preferred methods for preparing nano- or microparticles that may be applied to the albumin, variant, fragment, fusion, conjugate or associate thereof according to the invention is disclosed in WO 2004/071536 or WO2008/007146 or Oner & Groves (Pharmaceutical Research, Vol 10(9), 1993, pages 1387 to 1388) which are incorporated herein by reference. Preferably the average diameter of a nano-particle is from 5 to 1000 nm, more preferably 5, 10, 20, 30, 40, 50, 80, 100, 130, 150, 200, 300, 400, 500, 600, 700, 800, 900, or 999 to 5, 10, 20, 30, 40, 50, 80, 100, 130, 150, 200, 300, 400, 500, 600, 700, 800, 900,

or 1000 nm. An advantage of a microparticle less than 200 nm diameter, and more particularly less than 130 nm, is that is amenable to sterilization by filtration through a 0.2 μm (micron) filter. Preferably, the average diameter of a microparticle is from 1000 nm (1 μm (micron)) to 100 μm (micron), more preferably from 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 to 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 μm (micron).

[0205] Further preferences for the tenth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Uses

[0206] An eleventh aspect of the invention relates to use of a variant albumin, fragment, fusion or conjugate thereof or nanoparticle or associate thereof. Use may be, for example, in a method of treatment, prophylaxis, diagnosis or imaging. The variant albumin or fragments thereof or fusion polypeptides comprising variant albumin or fragments thereof according to the invention have the benefit that their binding affinity to FcRn and/or plasma half-life is altered compared to the parent or reference albumin or fragments thereof or fusion polypeptides comprising parent or reference albumin or fragments thereof. This has the advantage that the binding affinity to FcRn and/or plasma half-life of conjugates comprising variant albumin or a fragment thereof or fusion polypeptide comprising variant albumin or a fragment thereof, or an associate comprising variant albumin or a fragment thereof according to the invention can be selected in accordance with the particular therapeutic purpose.

[0207] In some situations, it would be advantageous to use an albumin, variant, fragment, fusion, conjugate or associate or composition thereof having a longer plasma half-life than the reference molecule or composition since this would have the benefit that the administration of the albumin, variant, fragment, fusion, conjugate or associate or composition thereof would be needed less frequently or at a reduced dose (and consequently with fewer side effects) compared to the situation where the reference molecule or composition was used. With respect to the use of a variant, fusion, conjugate, associate, nanoparticle, composition or polynucleotide the albumin moiety may comprise one more alterations as disclosed herein.

[0208] In other situations, it would be advantageous to use an albumin, variant, fragment, fusion, conjugate or associate or composition thereof having a shorter plasma half-life than the reference molecule or composition since this would have the benefit that the administration of the albumin, variant, fragment, fusion, conjugate or associate or composition thereof can be carried out at a higher dose compared to the situation where the reference molecule or composition was used with the benefit that the administered compound clears from the recipient more quickly than if the reference molecule or composition was used. With respect to the use of a variant, fusion, conjugate, associate, nanoparticle, composition or polynucleotide the albumin moiety may comprise one more alterations as disclosed herein.

[0209] For example for a conjugate, associate or fusion polypeptide used for imaging purposes in animals or human beings, where the imaging moiety has a very short half-life and a conjugate or a fusion polypeptide comprising HSA has a plasma half-life that is far longer than needed for the imaging purposes it would be advantageous to use a variant albumin or fragment thereof of the invention having a shorter plasma half-life than the parent or reference albumin or fragment thereof, to provide conjugates of fusion polypeptides having a plasma half-life that is sufficiently long for the imaging purpose but sufficiently short to be cleared from the body of the particular patient on which it is applied.

[0210] In another example for a conjugate, an associate or fusion polypeptide comprising a therapeutic compound effective to treat or alleviate a particular condition in a patient in need for such a treatment it would be advantageous to use the variant albumin or fragment thereof having a longer plasma half-life than the parent or reference albumin or fragment thereof, to provide associates or conjugates or fusion polypeptides having longer plasma half-lives which would have the benefit that the administration of the associate or conjugate or fusion polypeptide of the invention would be needed less frequently or reduced dose with less side effects compared to the situation where the parent or reference albumin or associates thereof or fragment thereof was used. For example, the invention provides a method of treating a proliferative disease in an individual, comprising administering the individual an effective amount of an associate according to the invention in which the associate comprises a taxane, a taxol or taxol derivative (e.g. paclitaxel).

[0211] In a further aspect the invention relates to compositions comprising the variant albumin, associates thereof or fragment thereof, variant albumin fragment or associates thereof or fusion polypeptide comprising variant albumin or fragment thereof according to the invention. The compositions are preferably pharmaceutical compositions. The composition may be prepared using techniques known in the area such as disclosed in recognized handbooks within the pharmaceutical field. Since the albumin, variant, fragment, fusion, conjugate or associate thereof has a binding affinity to FcRn and/or plasma half-life which is modulated (*i.e.* stronger or weaker and/or longer or shorter) than that of a reference molecule, the composition also has a binding affinity to FcRn and/or modulated (*i.e.* altered) plasma half-life relative to an equivalent composition comprising the reference molecule in place of the albumin, variant, fragment, fusion, conjugate or associate thereof as described herein. The composition may be a vaccine. The polypeptide according to

the invention may be an active pharmaceutical or an excipient. Optionally, the composition is provided in unit dosage form.

[0212] Preferably the albumin, variant, fragment, fusion, conjugate or associate thereof has a plasma half-life that is longer than the plasma half-life of the reference molecule e.g. the same composition except that the albumin component (e.g. albumin, variant, fragment, fusion, conjugate or associate) is wild-type albumin (e.g. HSA) or a variant, fragment, fusion, conjugate or associate.

[0213] In a particular embodiment the compositions comprise a variant albumin or a fragment thereof according to the invention and a compound comprising a pharmaceutically beneficial moiety and an albumin binding domain (ABD). According to the invention ABD means a site, moiety or domain capable of binding to circulating albumin *in vivo* and thereby conferring transport in the circulation of the ABD and any compound or moiety bound to said ABD. ABD's are known in the art and have been shown to bind very tight to albumin so a compound comprising an ABD bound to albumin will to a certain extent behave as a single molecule. The inventors have realized by using the variant albumin or fragment thereof according to the invention together with a compound comprising a pharmaceutically beneficial moiety and an ABD makes it possible to alter the binding affinity to FcRn and/or plasma half-life of the compound comprising a pharmaceutically beneficial moiety and an ABD compared to the situation where said compound were injected as such in a patient having need thereof or administered in a formulation comprising natural albumin or a fragment thereof.

[0214] The variant albumin or fragments thereof, conjugates comprising variant albumin or a fragment thereof or fusion polypeptide comprising variant albumin or a fragment thereof, or an associate comprising variant albumin or a fragment thereof according to the invention may also be incorporated into nano- or microparticles using techniques well known within the art. A preferred method for preparing nano- or microparticles that may be applied to the variant albumins or fragments thereof according to the invention is disclosed in WO 2004/071536 or WO2008/007146 or Oner & Groves (Pharmaceutical Research, Vol 10(9), 1993, pages 1387 to 1388) which are incorporated herein by reference.

[0215] Further preferences for the eleventh aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Method for altering the FcRn-binding affinity or half-life of a molecule

[0216] A twelfth aspect of the invention provides a method for altering the FcRn-binding affinity or half-life of a molecule comprising:

(a) where the molecule is a polypeptide, fusing or conjugating the molecule to a polypeptide disclosed herein or to a conjugate disclosed herein; associating the molecule to a polypeptide disclosed herein or to a conjugate disclosed herein; incorporating the molecule in a nanoparticle disclosed herein or a composition disclosed herein;

(b) where the molecule is not a polypeptide, conjugating the molecule to a polypeptide disclosed herein or to a conjugate disclosed herein; associating the molecule to a polypeptide disclosed herein or to a conjugate a disclosed herein; incorporating the molecule in a nanoparticle disclosed herein or a composition disclosed herein.

[0217] Examples of 'molecule' include those useful in therapy, prophylaxis (including those used in vaccines either as an active pharmaceutical ingredient or as an excipient), imaging and diagnosis, such as those described herein.

[0218] Further preferences for the twelfth aspect of the invention include those of the first aspect of the invention and those provided below this twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

[0219] Preferences for all aspects of the invention are provided below. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

[0220] The variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition may have a plasma half-life that is either longer or shorter, preferably longer, than the plasma half-life than a corresponding albumin or a fragment thereof or fusion polypeptides comprising albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition or a binding to FcRn that is stronger or weaker, preferably weaker. Preferably the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition has a plasma half-life that is longer than the plasma half-life of HSA or the corresponding albumin or a fragment thereof or fusion polypeptides comprising albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition.

[0221] Alternatively, this may be expressed as the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition

having a KD to FcRn (e.g. shFcRn) that is lower than the corresponding KD for HSA to FcRn or the corresponding fragment thereof or fusion polypeptide comprising HSA or fragment thereof. Preferably, the KD for the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition is less than 0.9X KD for HSA to FcRn, more preferred less than 0.5X KD for HSA to FcRn, more preferred less than 0.1X KD for HSA to FcRn, even more preferred less than 0.05X KD for HSA to FcRn, even more preferred less than 0.02X KD for HSA to FcRn and most preferred less than 0.01X KD for HSA to FcRn (where X means 'multiplied by'). The KD of the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition may be between the KD of WT albumin (e.g. SEQ ID No. 2) for FcRn and the KD of HSA K573P (SEQ ID No. 3) for FcRn. Such KDs represent binding affinities that are higher than the binding affinity between HSA and FcRn. A higher binding affinity indicates a longer half-life, for example plasma half-life.

[0222] Alternatively, the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition has a plasma half-life that is shorter than the plasma half-life of HSA or the corresponding fragment thereof or fusion polypeptide comprising HSA or fragment thereof.

[0223] This may be expressed as the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition having a KD to FcRn that is higher than the corresponding KD for HSA to FcRn or the corresponding of albumin or a fragment thereof or fusion polypeptides comprising albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition. Preferably, the KD for the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, or a conjugate comprising a variant of albumin or a fragment thereof is more than 2X KD for HSA to FcRn, more preferred more than 5X KD for HSA to FcRn, more preferred more than 10X KD for HSA to FcRn, even more preferred more than 25X KD for HSA to FcRn, even most preferred more than 50X KD for HSA to FcRn. The variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition may be a null binder to FcRn.

[0224] The variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, or a conjugate or nanoparticle or associate or composition comprising a variant of albumin or a fragment thereof is preferably the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, or a conjugate or nanoparticle or associate or composition comprising a variant of albumin or a fragment thereof according to the invention. A lower binding affinity indicates a shorter half-life, for example plasma half-life.

[0225] One advantage of the invention is that it allows the half-life of albumin, a variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition to be tailored in order to achieve a binding affinity or half-life which meets the needs of the user.

[0226] When determining and/or comparing KD, one or more (and preferably all) of the following parameters may be used:

Instrument: Biacore 3000 instrument (GE Healthcare)

Flow cell: CM5 sensor chip

FcRn: human FcRn, preferably soluble human FcRn, optionally coupled to a tag such as GST or His, most preferably His such as 6 histidines at the C-terminus of the beta-2-microglobulin (SEQ ID NO: 31).

Quantity of FcRn: 1200-2500 RU

Coupling chemistry: amine coupling chemistry (e.g. as described in the protocol provided by the manufacturer of the instrument).

Coupling method: The coupling may be performed by injecting 20 µg/ml of the protein in 10 mM sodium acetate pH 5.0 (GE Healthcare). Phosphate buffer (67 mM phosphate buffer, 0.15 M NaCl, 0.005% Tween 20) at pH 5.5) may be used as running buffer and dilution buffer. Regeneration of the surfaces may be done using injections of HBS-EP buffer (0.01 M HEPES, 0.15 M NaCl, 3 mM EDTA, 0.005% surfactant P20) at pH 7.4 (Biacore AB).

Quantity of injection of test molecule (e.g. HSA or variant) 20-0.032µM

Flow rate of injection: constant, e.g. 30 µl/ml

Temperature of injection: 25 °C

Data evaluation software: BIAevaluation 4.1 software (BIAcore AB).

The preferred method for determining KD is provided in Example 2.

[0227] The invention discloses that one or more (several) positions in Domain I in combination with one or more (several) positions in Domain III in SEQ ID NO: 2 (and therefore equivalent positions in albumins and fragments from human serum and albumin and non-human serum albumins) may be altered in order to modulate (increase or decrease) the binding affinity and/or half-life e.g. plasma half-life of an albumin, fragment, fusion, conjugate, associate, nanoparticle

or composition. An alteration may be a substitution, insertion or deletion. Substitution is preferred.

[0228] A substitution or insertion may or may not comprise introduction of a conserved amino acid, *i.e.* conserved in relation to the amino acid at the position of interest. Examples of conserved amino acids are shown by the groups of Fig. 3: aliphatic, aromatic, hydrophobic, charged, polar, positive, tiny and small.

[0229] At position 82 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to Q, D, A, even more preferred to D, A and most preferred to A. In SEQ ID NO: 2 the native amino acid at position 82 is glutamic acid, therefore a substitution to glutamic acid is not preferred.

[0230] At position 83 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, K, S, even more preferred to N, K and most preferred to N. In SEQ ID NO: 2 the native amino acid at position 83 is threonine, therefore a substitution to threonine is not preferred.

[0231] At position 111 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, E, Q, D, G, H, even more preferred to E, Q and most preferred to E. In SEQ ID NO: 2 the native amino acid at position 111 is asparagine, therefore a substitution to asparagine is not preferred.

[0232] At position 112 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to F, Y, W, even more preferred to F, Y and most preferred to F. In SEQ ID NO: 2 the native amino acid at position 112 is leucine, therefore a substitution to leucine is not preferred.

[0233] At position 573 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to P, Y, W, H, F, T, I or V, even more preferred to P, Y or W and most preferred to P. In SEQ ID NO: 2 the native amino acid at position 573 is lysine, therefore a substitution to lysine is not preferred.

[0234] It is preferred that the alteration at position 82 is conserved relative to A. It is preferred that the alteration at position 83 is conserved relative to N. It is preferred that the alteration at position 111 is conserved relative to E. It is preferred that the alteration at position 112 is conserved relative to F. It is preferred that the alteration at position 573 is conserved relative to P.

[0235] Particularly preferred albumin variants comprise substitutions T83N/N111E (*e.g.* SEQ ID NO: 32); T83N/N111E/K573P (*e.g.* SEQ ID NO: 33); T83N/K573P (*e.g.* SEQ ID NO: 34); T83K/K573P (*e.g.* SEQ ID NO: 38); E82A/K573P (*e.g.* SEQ ID NO: 39); L112F/K573P (*e.g.* SEQ ID NO: 40); E82D/K573P (*e.g.* SEQ ID NO: 43); P110G/K573P (*e.g.* SEQ ID NO: 44); N111D/K573P (*e.g.* SEQ ID NO: 60); N111G/K573P (*e.g.* SEQ ID NO: 61); N111H/K573P (*e.g.* SEQ ID NO: 62); E425A/K573P (*e.g.* SEQ ID NO: 64); E505Q/K573P (*e.g.* SEQ ID NO: 65); T527M/K573P (*e.g.* SEQ ID NO: 66); N111E/K573P (*e.g.* SEQ ID NO: 68); K534V/K573P (*e.g.* SEQ ID NO: 73); N111Q/K573P (*e.g.* SEQ ID NO: 74) which are described with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0236] Also, an albumin variant according to the invention may comprise one or more (several) alterations at positions selected from 78 to 88 and/or 105 to 120 and/or 425, 505, 510, 512, 524, 527, 531, 534, 569, 575 of HSA (SEQ ID NO: 2) or equivalent positions of other albumins. Preferred alterations are substitutions such as those described for these positions in the first aspect of the invention. Particularly preferred substitutions include D108A (SEQ ID NO: 59); D108E (*e.g.* SEQ ID NO: 70); N109K (*e.g.* SEQ ID NO: 69); P110G (*e.g.* SEQ ID NO: 42); N111D (*e.g.* SEQ ID NO: 46); N111E (*e.g.* SEQ ID NO: 67); N111G (*e.g.* SEQ ID NO: 48); N111H (*e.g.* SEQ ID NO: 49); N111K (*e.g.* SEQ ID NO: 54); L112F (*e.g.* SEQ ID NO: 37); E425A (*e.g.* SEQ ID NO: 63); E425K (*e.g.* SEQ ID NO: 55); E505Q (*e.g.* SEQ ID NO: 45); H510D (*e.g.* SEQ ID NO: 57); D512E (*e.g.* SEQ ID NO: 50); K524A (*e.g.* SEQ ID NO: 51); T527A (*e.g.* SEQ ID NO: 52); T527M (*e.g.* SEQ ID NO: 47); E531H (*e.g.* SEQ ID NO: 53); K534V (*e.g.* SEQ ID NO: 56); A569S (*e.g.* SEQ ID NO: 58); L575F (*e.g.* SEQ ID NO: 72); E82A (*e.g.* SEQ ID NO: 36); E82D (*e.g.* SEQ ID NO: 41); T83K (*e.g.* SEQ ID NO: 35); T83N (*e.g.* SEQ ID NO: 71) which are described with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprising one or more (several) alterations may comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0237] Advantageously, the polypeptide retains substantially the same tertiary structure (or, for a fragment, the relevant part of the structure) as a reference or parent albumin such as HSA. The skilled person understands the term 'substantially the same tertiary structure' bearing in mind that some degree of variation in tertiary structure is expected as all proteins have some degree of structural flexibility. This applies particularly to polypeptides having a higher binding affinity to FcRn than the parent or reference albumin (*e.g.* HSA) has to FcRn.

[0238] One or more (several) of the His residues may or may not be maintained relative to the parent albumin. For example, with reference to SEQ ID NO: 2, one or more (several) of the following His residues may be maintained: 3, 9, 39, 67, 105, 128, 146, 242, 247, 288, 338, 367, 440, 464, 510, and/or 535. One or more (several), preferably all, of the His residues in domain I are maintained (*i.e.* 3, 9, 39, 67, 105, 128, 146.). One or more (several), preferably all, of the His residues in domain II are maintained (*i.e.* 242, 247, 288, 338, 367). One or more (several), preferably all, of the His

residues in domain III are maintained (*i.e.* 440, 464, 510, 535). One or more (several) or all three of His 464, 510, 535 may be maintained.

[0239] It is preferred that at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 of the disulphide bonds of the albumin are maintained in the polypeptide. For a polypeptide derived from a full length albumin, it is preferred that all disulphide bonds usually present in that albumin are maintained. For a polypeptide derived from a fragment of albumin, it is preferred that all disulphide bonds usually present in that fragment are maintained. It is preferred that Cys34 (or equivalent in non-human albumins) is maintained.

[0240] For all aspects of the invention fusion partner polypeptides and/or conjugates may comprise one or more (several) of: 4-1BB ligand, 5-helix, A human C-C chemokine, A human L105 chemokine, A human L105 chemokine designated huL105_3, A monokine induced by gamma-interferon (MIG), A partial CXCR4B protein, A platelet basic protein (PBP), α 1-antitrypsin, ACRP-30 Homologue; Complement Component C1q C, Adenoid-expressed chemokine (ADEC), aFGF; FGF-1, AGF, AGF Protein, albumin, an etoposide, angiostatin, Anthrax vaccine, Antibodies specific for collapsin, antistatin, Anti-TGF beta family antibodies, antithrombin III, APM-1; ACRP-30; Famoxin, apo-lipoprotein species, Arylsulfatase B, b57 Protein, BCMA, Beta-thromboglobulin protein (beta-TG), bFGF; FGF2, Blood coagulation factors, BMP Processing Enzyme Furin, BMP-10, BMP-12, BMP-15, BMP-17, BMP-18, BMP-2B, BMP-4, BMP-5, BMP-6, BMP-9, Bone Morphogenic Protein-2, calcitonin, Calpain-10a, Calpain-10b, Calpain-10c, Cancer Vaccine, Carboxypeptidase, C-C chemokine, MCP2, CCR5 variant, CCR7, CCR7, CD11a Mab, CD137; 4-1BB Receptor Protein, CD20 Mab, CD27, CD27L, CD30, CD30 ligand, CD33 immunotoxin, CD40, CD40L, CD52 Mab, Cerebus Protein, Chemokine Eotaxin., Chemokine hIL-8, Chemokine hMCP1, Chemokine hMCP1a, Chemokine hMCP1b, Chemokine hMCP2, Chemokine hMCP3, Chemokine hSDF1b, Chemokine MCP-4, chemokine TECK and TECK variant, Chemokine-like protein IL-8M1 Full-Length and Mature, Chemokine-like protein IL-8M10 Full-Length and Mature, Chemokine-like protein IL-8M3, Chemokine-like protein IL-8M8 Full-Length and Mature, Chemokine-like protein IL-8M9 Full-Length and Mature, Chemokine-like protein PF4-414 Full-Length and Mature, Chemokine-like protein PF4-426 Full-Length and Mature, Chemokine-like protein PF4-M2 Full-Length and Mature, Cholera vaccine, Chondromodulin-like protein, c-kit ligand; SCF; Mast cell growth factor; MGF; Fibrosarcoma-derived stem cell factor, CNTF and fragment thereof (such as CNTF α 15'(AxokineTM)), coagulation factors in both pre and active forms, collagens, Complement C5 Mab, Connective tissue activating protein-III, CTAA16.88 Mab, CTAP-III, CTLA4-Ig, CTLA-8, CXC3, CXC3, CXCR3; CXC chemokine receptor 3, cyanovirin-N, Darbepoetin, designated exodus, designated huL105_7, DIL-40, DNase, EDAR, EGF Receptor Mab, ENA-78, Endostatin, Eotaxin, Epithelial neutrophil activating protein-78, EPO receptor; EPOR, erythropoietin (EPO) and EPO mimics, Eutropin, Exodus protein, Factor IX, Factor VII, Factor VIII, Factor X and Factor XIII, FAS Ligand Inhibitory Protein (DcR3), FasL, FasL, FasL, FGF, FGF-12; Fibroblast growth factor homologous factor-1, FGF-15, FGF-16, FGF-18, FGF-3; INT-2, FGF-4; gelonin, HST-1; HBGF-4, FGF-5, FGF-6; Heparin binding secreted transforming factor-2, FGF-8, FGF-9; Glia activating factor, fibrinogen, flt-1, flt-3 ligand, Follicle stimulating hormone Alpha subunit, Follicle stimulating hormone Beta subunit, Follitropin, Fractalkine, fragment. myofibrillar protein Troponin I, FSH, Galactosidase, Galectin-4, G-CSF, GDF-1, Gene therapy, Glioma-derived growth factor, glucagon, glucagon-like peptides, Glucocerebrosidase, glucose oxidase, Glucosidase, Glycodelin-A; Progesterone-associated endometrial protein, GM-CSF, gonadotropin, Granulocyte chemotactic protein-2 (GCP-2), Granulocyte-macrophage colony stimulating factor, growth hormone, Growth related oncogene-alpha (GRO-alpha), Growth related oncogene-beta (GRO-beta), Growth related oncogene-gamma (GRO-gamma), hAPO-4; TROY, hCG, Hepatitis B surface Antigen, Hepatitis B Vaccine, HER2 Receptor Mab, hirudin, HIV gp120, HIV gp41, HIV Inhibitor Peptide, HIV Inhibitor Peptide, HIV Inhibitor Peptide, HIV protease inhibiting peptides, HIV-1 protease inhibitors, HPV vaccine, Human 6CKine protein, Human Act-2 protein, Human adipogenesis inhibitory factor, human B cell stimulating factor-2 receptor, Human beta-chemokine H1305 (MCP-2), Human C-C chemokine DGWCC, Human CC chemokine ELC protein, Human CC type chemokine interleukin C, Human CCC3 protein, Human CCF18 chemokine, Human CC-type chemokine protein designated SLC (secondary lymphoid chemokine), Human chemokine beta-8 short forms, Human chemokine C10, Human chemokine CC-2, Human chemokine CC-3, Human chemokine CCR-2, Human chemokine Ckbeta-7, Human chemokine ENA-78, Human chemokine eotaxin, Human chemokine GRO alpha, Human chemokine GROalpha, Human chemokine GRObeta, Human chemokine HCC-1, Human chemokine HCC-1, Human chemokine I-309, Human chemokine IP-10, Human chemokine L105_3, Human chemokine L105_7, Human chemokine MIG, Human chemokine MIG-beta protein, Human chemokine MIP-1alpha, Human chemokine MIP1beta, Human chemokine MIP-3alpha, Human chemokine MIP-3beta, Human chemokine PF4, Human chemokine protein 331D5, Human chemokine protein 61164, Human chemokine receptor CXCR3, Human chemokine SDF1alpha, Human chemokine SDF1beta, Human chemokine ZSIG-35, Human Chr19Kine protein, Human CKbeta-9, Human CKbeta-9, Human CX3C 111 amino acid chemokine, Human DNAX interleukin-40, Human DVic-1 C-C chemokine, Human EDIRF I protein sequence, Human EDIRF II protein sequence, Human eosinocyte CC type chemokine eotaxin, Human eosinophil-expressed chemokine (EEC), Human fast twitch skeletal muscle troponin C, Human fast twitch skeletal muscle troponin I, Human fast twitch skeletal muscle Troponin subunit C, Human fast twitch skeletal muscle Troponin subunit I Protein, Human fast twitch skeletal muscle Troponin subunit T, Human fast twitch skeletal muscle troponin T, Human foetal spleen expressed chemokine, FSEC, Human GM-CSF receptor, Human

gro-alpha chemokine, Human gro-beta chemokine, Human gro-gamma chemokine, Human IL-16 protein, Human IL-1RD10 protein sequence, Human IL-1RD9, Human IL-5 receptor alpha chain, Human IL-6 receptor, Human IL-8 receptor protein hIL8RA, Human IL-8 receptor protein hIL8RB, Human IL-9 receptor protein, Human IL-9 receptor protein variant #3, Human IL-9 receptor protein variant fragment, Human IL-9 receptor protein variant fragment#3, Human interleukin 1 delta, Human Interleukin 10, Human Interleukin 10, Human interleukin 18, Human interleukin 18 derivatives, Human interleukin-1 beta precursor, Human interleukin-1 beta precursor., Human interleukin-1 receptor accessory protein, Human interleukin-1 receptor antagonist beta, Human interleukin-1 type-3 receptor, Human Interleukin-10 (precursor), Human Interleukin-10 (precursor), Human interleukin-11 receptor, Human interleukin-12 40 kD subunit, Human interleukin-12 beta-1 receptor, Human interleukin-12 beta-2 receptor, Human Interleukin-12 p35 protein, Human Interleukin-12 p40 protein, Human interleukin-12 receptor, Human interleukin-13 alpha receptor, Human interleukin-13 beta receptor, Human interleukin-15, Human interleukin-15 receptor from clone P1, Human interleukin-17 receptor, Human interleukin-18 protein (IL-18), Human interleukin-3, human interleukin-3 receptor, Human interleukin-3 variant, Human interleukin-4 receptor, Human interleukin-5, Human interleukin-6, Human interleukin-7, Human interleukin-7., Human interleukin-8 (IL-8), Human intracellular IL-1 receptor antagonist, Human IP-10 and HIV-1 gp120 hypervariable region fusion protein, Human IP-10 and human Muc-1 core epitope (VNT) fusion protein, human liver and activation regulated chemokine (LARC), Human Lkn-1 Full-Length and Mature protein, Human mammary associated chemokine (MACK) protein Full-Length and Mature, Human mature chemokine Ckbeta-7, Human mature gro-alpha, Human mature gro-gamma polypeptide used to treat sepsis, Human MCP-3 and human Muc-1 core epitope (VNT) fusion protein, Human MI10 protein, Human MI1A protein, Human monocyte chemoattractant factor hMCP-1, Human monocyte chemoattractant factor hMCP-3, Human monocyte chemotactic proprotein (MCP-3) sequence, Human neurotactin chemokine like domain, Human non-ELR CXC chemokine H174, Human non-ELR CXC chemokine IP10, Human non-ELR CXC chemokine Mig, Human PAI-1 mutants, Human protein with IL-16 activity, Human protein with IL-16 activity, Human secondary lymphoid chemokine (SLC), Human SISD protein, Human STCP-1, Human stromal cell-derived chemokine, SDF-1, Human T cell mixed lymphocyte reaction expressed chemokine (TMEC), Human thymus and activation regulated cytokine (TARC), Human thymus expressed, Human TNF-alpha, Human TNF-alpha, Human TNF-beta (LT-alpha), Human type CC chemokine eotaxin 3 protein sequence, Human type II interleukin-1 receptor, Human wild-type interleukin-4 (hIL-4) protein, Human ZCHEMO-8 protein, Humanized Anti-VEGF Antibodies, and fragments thereof, Humanized Anti-VEGF Antibodies, and fragments thereof, Hyaluronidase, ICE 10 kD subunit., ICE 20 kD subunit., ICE 22 kD subunit., Iduronate-2-sulfatase, Iduronidase, IL-1 alpha, IL-1 beta, IL-1 inhibitor (IL-1i), IL-1 mature, IL-10 receptor, IL-11, IL-11, IL-12 p40 subunit., IL-13, IL-14, IL-15, IL-15 receptor, IL-17, IL-17 receptor, IL-17 receptor, IL-17 receptor, IL-19, IL-1i fragments, IL-1-receptor antagonist, IL-21 (TIF), IL-3 containing fusion protein., IL-3 mutant proteins, IL-3 variants, IL-3 variants, IL-4, IL-4 mutein, IL-4 mutein Y124G, IL-4 mutein Y124X, IL-4 muteins, IL-5 receptor, IL-6, IL-6 receptor, IL-7 receptor clone, IL-8 receptor, IL-9 mature protein variant (Met117 version), immunoglobulins or immunoglobulin-based molecules or fragment of either (e.g. a Small Modular ImmunoPharmaceutical™ ("SMIP") or dAb, Fab' fragments, F(ab')2, scAb, scFv or scFv fragment), including but not limited to plasminogen, Influenza Vaccine, Inhibin alpha, Inhibin beta, insulin, insulin-like growth factor, Integrin Mab, inter-alpha trypsin inhibitor, inter-alpha trypsin inhibitor, Interferon gamma-inducible protein (IP-10), interferons (such as interferon alpha species and sub-species, interferon beta species and sub-species, interferon gamma species and sub-species), interferons (such as interferon alpha species and sub-species, interferon beta species and sub-species, interferon gamma species and sub-species), Interleukin 6, Interleukin 8 (IL-8) receptor, Interleukin 8 receptor B, Interleukin-1alpha, Interleukin-2 receptor associated protein p43, interleukin-3, interleukin-4 muteins, Interleukin-8 (IL-8) protein., interleukin-9, Interleukin-9 (IL-9) mature protein (Thr117 version), interleukins (such as IL10, IL11 and IL2), interleukins (such as IL10, IL11 and IL2), Japanese encephalitis vaccine, Kalikrein Inhibitor, Keratinocyte growth factor, Kunitz domain protein (such as aprotinin, amyloid precursor protein and those described in WO 03/066824, with or without albumin fusions), Kunitz domain protein (such as aprotinin, amyloid precursor protein and those described in WO 03/066824, with or without albumin fusions), LACI, lactoferrin, Latent TGF-beta binding protein II, leptin, Liver expressed chemokine-1 (LVEC-1), Liver expressed chemokine-2 (LVEC-2), LT-alpha, LT-beta, Luteinization Hormone, Lyme Vaccine, Lymphotactin, Macrophage derived chemokine analogue MDC (n+1), Macrophage derived chemokine analogue MDC-eyfy, Macrophage derived chemokine analogue MDC-yl, Macrophage derived chemokine, MDC, Macrophage-derived chemokine (MDC), Maspin; Protease Inhibitor 5, MCP-1 receptor, MCP-1a, MCP-1b, MCP-3, MCP-4 receptor, M-CSF, Melanoma inhibiting protein, Membrane-bound proteins, Met117 human interleukin 9, MIP-3 alpha, MIP-3 beta, MIP-Gamma, MIRAP, Modified Rantes, monoclonal antibody, MP52, Mutant Interleukin 6 S176R, myofibrillar contractile protein Troponin I, Natriuretic Peptide, Nerve Growth Factor-beta, Nerve Growth Factor-beta2, Neuropilin-1, Neuropilin-2, Neurotactin, Neurotrophin-3, Neurotrophin-4, Neurotrophin-4a, Neurotrophin-4b, Neurotrophin-4c, Neurotrophin-4d, Neutrophil activating peptide-2 (NAP-2), NOGO-66 Receptor, NOGO-A, NOGO-B, NOGO-C, Novel beta-chemokine designated PTEC, N-terminal modified chemokine GroHEK/hSDF-1alpha, N-terminal modified chemokine GroHEK/hSDF-1beta., N-terminal modified chemokine met-hSDF-1 alpha, N-terminal modified chemokine met-hSDF-1 beta, OPGL, Osteogenic Protein-1; OP-1; BMP-7, Osteogenic Protein-2, OX40; ACT-4, OX40L, Oxytocin (Neurophysin I), parathyroid hormone, Patched, Patched-2, PDGF-D, Pertussis toxoid, Pituitary expressed chemokine (PGEC), Pla-

cental Growth Factor, Placental Growth Factor-2, Plasminogen Activator Inhibitor-1; PAI-1, Plasminogen Activator Inhibitor-2; PAI-2, Plasminogen Activator Inhibitor-2; PAI-2, Platelet derived growth factor, Platelet derived growth factor Bv-sis, Platelet derived growth factor precursor A, Platelet derived growth factor precursor B, Platelet Mab, platelet-derived endothelial cell growth factor (PD-ECGF), Platelet-Derived Growth Factor A chain, Platelet-Derived Growth Factor B chain, polypeptide used to treat sepsis, Preproapolipoprotein "milano" variant, Preproapolipoprotein "paris" variant, pre-thrombin, Primate CC chemokine "ILINCK", Primate CXC chemokine "IBICK", proinsulin, Prolactin, Prolactin2, prosaptide, Protease inhibitor peptides, Protein C, Protein S, pro-thrombin, prourokinase, RANTES, RANTES 8-68, RANTES 9-68, RANTES peptide, RANTES receptor, Recombinant interleukin-16, Resistin, restrictocin, Retroviral protease inhibitors, ricin, Rotavirus Vaccine, RSV Mab, saporin, sarcin, Secreted and Transmembrane polypeptides, Secreted and Transmembrane polypeptides, serum cholinesterase, serum protein (such as a blood clotting factor), Soluble BMP Receptor Kinase Protein-3, Soluble VEGF Receptor, Stem Cell Inhibitory Factor, Straphylococcus Vaccine, Stromal Derived Factor-1 alpha, Stromal Derived Factor-1 beta, Substance P (tachykinin), T1249 peptide, T20 peptide, T4 Endonuclease, TACI, Tarc, TGF-beta 1, TGF-beta 2, Thr117 human interleukin 9, thrombin, thrombopoietin, Thrombopoietin derivative1, Thrombopoietin derivative2, Thrombopoietin derivative3, Thrombopoietin derivative4, Thrombopoietin derivative5, Thrombopoietin derivative6, Thrombopoietin derivative7, Thymus expressed chemokine (TECK), Thyroid stimulating Hormone, tick anticoagulant peptide, Tim-1 protein, TNF-alpha precursor, TNF-R, TNF-RII; TNF p75 Receptor; Death Receptor, tPA, transferrin, transforming growth factor beta, Troponin peptides, Truncated monocyte chemotactic protein 2 (6-76), Truncated monocyte chemotactic protein 2 (6-76), Truncated RANTES protein (3-68), tumour necrosis factor, Urate Oxidase, urokinase, Vasopressin (Neurophysin II), VEGF R-3; flt-4, VEGF Receptor; KDR; flk-1, VEGF-110, VEGF-121, VEGF-138, VEGF-145, VEGF-162, VEGF-165, VEGF-182, VEGF-189, VEGF-206, VEGF-D, VEGF-E; VEGF-X, von Willebrand's factor, Wild type monocyte chemotactic protein 2, Wild type monocyte chemotactic protein 2, ZTGF-beta 9, alternative antibody scaffolds e.g. anticalin(s), adnectin(s), fibrinogen fragment(s), nanobodies such as camelid nanobodies, infestin, and/or any of the molecules mentioned in WO01/79271 (particularly page 9 and/or Table 1), WO 2003/59934 (particularly Table 1), WO03/060071 (particularly Table 1) or WO01/079480 (particularly Table 1) (each incorporated herein by reference in their entirety).

[0241] Furthermore, conjugates may comprise one or more (several) of chemotherapy drugs such as: 13-cis-Retinoic Acid, 2-CdA, 2-Chlorodeoxyadenosine, 5-Azacididine, 5-Fluorouracil, 5-FU, 6-Mercaptopurine, 6-MP, 6-TG, 6-Thioguanine, A, Abraxane, Accutane®, Actinomycin-D, Adriamycin®, Adrucil®, Agrylin®, Ala-Cort®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ®, Alkeran®, All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron®, Anastrozole, Arabinosylcytosine, Ara-C, Aranesp®, Aredia®, Arimidex®, Aromasin®, Arranon®, Arsenic Trioxide, Asparaginase, ATRA, Avastin®, Azacididine, BCG, BCNU, Bevacizumab, Bexarotene, BEXXAR®, Bicalutamide, BiCNU, Blenoxane®, Bleomycin, Bortezomib, Busulfan, Busulfex®, C225, Calcium Leucovorin, Campath®, Camptosar®, Camptothecin-11, Capecitabine, Carac™, Carboplatin, Carmustine, Carmustine Wafer, Casodex®, CC-5013, CCNU, CDDP, CeeNU, Cerubidine®, Cetuximab, Chlorambucil, Cisplatin, Citrovorum Factor, Cladribine, Cortisone, Cosmegen®, CPT-11, Cyclophosphamide, Cytadren®, Cytarabine, Cytarabine Liposomal, Cytosar-U®, Cytoxan®, Dacarbazine, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome®, Decadron, Decitabine, Delta-Cortef®, Deltasone®, Denileukin diftitox, DepoCyt™, Dexamethasone, Dexamethasone acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodex, Docetaxel, Doxil®, Doxorubicin, Doxorubicin liposomal, Droxia™, DTIC, DTIC-Dome®, Duralone®, Efudex®, Eligard™, Ellence™, Eloxatin™, Elspar®, Emcyt®, Epirubicin, Epoetin alfa, Erbitux™, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethiol, Etopophos®, Etoposide, Etoposide Phosphate, Eulexin®, Evista®, Exemestane, Fareston®, Faslodex®, Femara®, Filgrastim, Floxuridine, Fludara®, Fludarabine, Fluoroplex®, Fluorouracil, Fluorouracil (cream), Fluoxymesterone, Flutamide, Folinic Acid, FUDR®, Fulvestrant, G-CSF, Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Gemzar®, Gleevec™, Gliadel® Wafer, GM-CSF, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Halotestin®, Herceptin®, Hexadrol, Hexalen®, Hexamethylmelamine, HMM, Hycamtin®, Hydrea®, Hydrocort Acetate®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab Tiuxetan, Idamycin®, Idarubicin, Ifex®, IFN-alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon alfa, Interferon Alfa-2b (PEG Conjugate), Interleukin-2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa®, Irinotecan, Isotretinoin, Kidrolase®, Lanacort®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine™, Leuprolide, Leurocristine, Leustatin™, Liposomal Ara-C, Liquid Pred®, Lomustine, L-PAM, L-Sarcosine, Lupron®, Lupron Depot®, M, Matulane®, Maxidex, Mechlorethamine, Mechlorethamine Hydrochloride, Medrolone®, Medrol®, Megace®, Megestrol, Megestrol Acetate, Melfalan, Mercaptopurine, Mesna, Mesnex™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticcorten®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol®, MTC, MTX, Mustargen®, Mustine, Mutamycin®, Myleran®, Mylocel™, Mylotarg®, Navelbine®, Nelarabine, Neosar®, Neulasta™, Neumega®, Neupogen®, Nexavar®, Nilandron®, Nilutamide, Nipent®, Nitrogen Mustard, Novaldex®, Novantrone®, Octreotide, Octreotide acetate, Oncospar®, Oncovin®, Ontak®, Onxal™, Oprevelkin, Orapred®, Orasone®, Oxaliplatin, a taxol or taxol derivative e.g. Paclitaxel or Paclitaxel Protein-bound, Pamidronate, Pani-

tumumab, Panretin®, Paraplatin®, Pediapred®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON™, PEG-L-asparaginase, PEMETREXED, Pentostatin, Phenylalanine Mustard, Platinol®, Platinol-AQ®, Prednisolone, Prednisone, Prelone®, Procarbazine, PROCIT®, Proleukin®, Prolifeprospan 20 with Carmustine Implant, Purinethol®, R, Raloxifene, Revlimid®, Rheumatrex®, Rituxan®, Rituximab, Roferon-A® (Interferon Alfa-2a), Rubex®, Rubidomycin hydrochloride, Sandostatin®, Sandostatin LAR®, Sargramostim, Solu-Cortef®, Solu-Medrol®, Sorafenib, SPRYCEL™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent®, Tamoxifen, Tarceva®, Targretin®, Taxol®, Taxotere®, Temodar®, Temozolomide, Teniposide, TESP, Thalidomide, Thalomid®, TheraCys®, Thioguanine, Thioguanine Tabloid®, Thio-phosphoamide, Thioplex®, Thiotepa, TICE®, Toposar®, Topotecan, Toremifene, Tositumomab, Trastuzumab, Tretinoin, Trexall™, Trisenox®, TSPA, TYKERB®, VCR, Vectibix™, Velban®, Velcade®, VePesid®, Vesanoid®, Viadur™, Viza®, Vinblastine, Vinblastine Sulfate, Vincasar Pfs®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vorinostat, VP-16, Vumon®, Xeloda®, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolinza, Zometa®; radiopharmaceuticals such as: Carbon-11, Carbon-14, Chromium-51, Cobalt-57, Cobalt-58, Erbium-169, Fluorine-18, Gallium-67, Gold-198, Indium-111, Indium-113m, Iodine-123, Iodine-125, Iodine-131, Iron-59, Krypton-81m, Nitrogen-13, Oxygen-15, Phosphorous-32, Rhenium-186, Rubidium-82, Samarium-153, Selenium-75, Strontium-89, Technetium-99m, Thallium-201, Tritium, Xenon-127, Xenon-133, Yttrium-90; imaging agents such as Gadolinium, magnetite, manganese, technetium, 1125, 1131, P32, Tl201, Iopamidol, PET-FDG.

[0242] Further fusion partners, conjugation partners and/or molecules for inclusion in a nanoparticle, associate or composition according to the invention include: acromegaly drugs e.g. somatuline, lanreotide, octreotide, Sandostatin; antithrombotics e.g. bivalirudin, Angiomax, dalteparin, Fragmin, enoxaparin, Lovenox, Drotrecogin alfa (e.g. Activated), Xigris, heparin; assisted reproductive therapy compounds e.g. choriogonadotropin, Ovidrel, follitropin, alpha/beta; enzymes e.g. hyaluronidase, Hylenex; diabetes drugs e.g. exenatide, Byetta, glucagon, insulin, liraglutide, albiglutide, GLP-1 agonists, exendin or an exendin analog; compounds useful in diagnosis e.g. protirelin, Thyrel TRH Thyphipone, secretin (e.g. synthetic human), Chirhistim, thyrotropin (e.g. alpha), Thyrogen' erythropoiesis drugs e.g. Darbepoetin alfa, Aranesp, Epoetin alfa, Epogen, Eprex, drugs for the treatment of genetic defects e.g. pegademase, drugs for the treatment of growth failure e.g. Adagen, mecasermin, rinfabate, drugs for the treatment of cystic fibrosis e.g. Dornase alfa, Pulmozyme, drugs for the treatment of metabolic disorders e.g. Agalsidase beta, Fabrazyme, alglucosidase alpha, Myozyme, Laronidase, Aldurazyme, drugs for the treatment of genital wart intralesional e.g. Interferon alfa-n3, Alferon N, drugs for the treatment of granulomatous disease e.g. Interferon gamma-1b, Actimmune; drugs for the treatment of growth failure e.g. pegvisomant, Somavert, somatropin, Genotropin, Nutropin, Humatrope, Serostim, Protropin; drugs for the treatment of heart failure e.g. nesiritide, Natrecor; drugs for the treatment of hemophilia e.g. a coagulation factor e.g. Factor VIII, Helixate FS, Kogenate FS, Factor IX, BeneFIX, Factor VIIa, Novoseven, desmopressin, Stimulate, DDAVP; hemopoietic drugs e.g. Filgrastim (G-CSF), Neupogen, Oprelvekin, Neumega, Pegfilgrastim, Neulasta, Sargramostim, Leukine; drugs for the treatment of hepatitis C e.g. Interferon alfa-2a, Roferon A, Interferon alfa-2b, Intron A, Interferon alfacon-1, Infergen, Peginterferon alfa-2a, Pegasys, Peginterferon alfa-2b, PEG-Intron; drugs for the treatment of HIV e.g. enfuvirtide, Fuzeon; Fabs e.g. Fab (antithrombin), Abciximab, ReoPro; monoclonal antibodies e.g. Daclizumab, Zenapax; antiviral monoclonal antibodies e.g. Palivizumab, Synagis; monoclonal antibodies for the treatment of asthma e.g. Omalizumab, Xolair; monoclonal antibodies for use in diagnostic imaging e.g. Arcitumomab, CEA-Scan, Capromab Pendetide, ProstaScint, Satumomab Pendetide, OncoScint CR/OV, Fabs for use in diagnostic imaging e.g. Nofetumomab, Verluma; immuno-suppressant monoclonal antibodies e.g. Basiliximab, Simulect, Muromonab-CD3, Orthoclone OKT3; monoclonal antibodies for the treatment of malignancy e.g. Alemtuzumab, Campath, Ibritumomab tiuxetan, Zevalin, Rituximab, Rituxan, Trastuzumab, Herceptin; monoclonal antibodies for the treatment of rheumatoid arthritis (RA) e.g. Adalimumab, Humira, Infliximab, Remicade; monoclonal antibodies for use as a radio-immuno-therapeutic e.g. Tositumomab and Iodine ¹³¹, Tositumomab, Bexxar; drugs for the treatment of macular degeneration e.g. pegaptanib, Macugen; drugs for the treatment of malignancy e.g. Aldesleukin, Proleukin, Interleukin-2, Asparaginase, Elspar, Rasburicase, Elitek, Denileukin diftitox, Ontak, Pegaspargase, Oncaspar, goserelin, leuprolide; drugs for the treatment of multiple sclerosis (MS) e.g. Glatiramer acetate (e.g. copolymer-1), Copaxone, Interferon beta-1a, Avonex, Interferon beta-1a, Rebif, Interferon beta-1b, Betaseron; drugs for the treatment of mucositis e.g. palifermin, Kepivance; drug for the treatment of dystonia e.g., neurotoxin, Botulinum Toxin Type A, BOTOX, BOTOX Cosmetic, Botulinum Toxin Type B, MYOBLOC; drugs for the treatment of osteoporosis e.g. teriparatide, Forteo; drugs for the treatment of psoriasis e.g. Alefacept, Amevive; drugs for the treatment of RA e.g. abatacept, Orencia, Anakinra, Kineret, Etanercept, Enbrel; thrombolytics e.g. Alteplase, Activase, recombinant tissue plasminogen activator (rtPA), Anistreplase, Eminase, Reteplase, Retavase, Streptokinase, Streptase, Tenecteplase, TNKase (tenecteplase), Urokinase, Abbokinase, Kinlytic; drugs for the treatment of osteoporosis e.g. calcitonin (e.g. salmon), Miacalcin, Fortical, drugs for the treatment of skin ulcers e.g. Becaplermin, Regranex, Collagenase, Santyl.

[0243] Such polypeptides and chemical compounds may be referred to as diagnostic moieties, therapeutic moieties, prophylactic moieties or beneficial moieties.

[0244] Preferably the fusion partner and/or conjugation partner is not an albumin, variant or fragment thereof.

[0245] One or more (several) therapeutic or prophylactic polypeptides may be fused to the N-terminus, the C-terminus

of albumin, inserted into a loop in the albumin structure or any combination thereof. It may or it may not comprise linker sequences separating the various components of the fusion polypeptide.

[0246] Teachings relating to fusions of albumin or a fragment thereof are known in the art and the skilled person will appreciate that such teachings can also be applied to the invention. WO 2001/79271A and WO 2003/59934 (incorporated herein by reference) also contain examples of therapeutic and prophylactic polypeptides that may be fused to albumin or fragments thereof, and these examples apply also to the invention.

[0247] Preferred embodiments of the invention include:

1. A polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or a fragment thereof, which polypeptide has one or more (several) alterations in Domain I of the albumin, fragment or fusion polypeptide and has one or more (several) alterations in Domain III of the albumin, fragment or fusion polypeptide and has an altered binding affinity to FcRn compared with the binding affinity of a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof to FcRn.

2. A polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or a fragment thereof, which polypeptide has one or more (several) alterations in Domain I of the albumin, fragment or fusion polypeptide and/or has one or more (several) alterations in Domain III of the albumin, fragment or fusion polypeptide and has an altered binding affinity to FcRn compared with the binding affinity of a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof to FcRn wherein the alteration(s) in Domain I are selected from positions corresponding to any of positions 78 to 120 of SEQ ID NO: 2 and the alteration(s) in Domain III are selected from positions corresponding to any of positions 425, 505, 510, 512, 524, 527, 531, 534, 569, 573, 575 of SEQ ID NO: 2.

3. The polypeptide according to embodiment 1 or 2 wherein the one or more (several) alterations in Domain I are selected from positions corresponding to any of positions from 78 to 88 and/or from any of 105 to 120 of SEQ ID NO: 2.

4. The polypeptide according to embodiment 1, 2 or 3 comprising alterations at positions corresponding to positions (a) 111 and 573; (b) 82 and 83; (c) 82 and 111; (d) 82 and 112; (e) 82 and 573; (f) 83 and 111; (g) 83 and 112; (h) 83 and 573; (i) 111 and 112; (j) 83, 111, and 573; (k) 112 and 573; (l) 82, 83, and 111; (m) 82, 83, and 112; (n) 82, 83, and 573; (o) 82, 111, and 112; (p) 82, 111, and 573; (q) 82, 112, and 573; (r) 83, 111, and 112; (s) 83, 112, and 573; (t) 111, 112, and 573; (u) 82, 83, 111, and 112; (v) 82, 83, 111, and 573; (w) 82, 83, 112, and 573; (x) 82, 111, 112, and 573; (y) 83, 111, 112, and 573; or (z) 82, 83, 111, 112, and 573 of SEQ ID NO: 2.

5. The polypeptide according any of embodiments 1 to 4 wherein the one or more (several) alterations in Domain I are selected from positions corresponding to 83 and/or 111 of SEQ ID NO: 2.

6. The polypeptide according to any of embodiments 1 to 5 wherein the alteration in Domain III is at a position corresponding to 573 of SEQ ID NO: 2.

7. The polypeptide according to any of embodiments 1 to 6 wherein the alteration in Domain I and/or the alteration in Domain III is a substitution.

8. The polypeptide of any of embodiments 2 to 7 wherein the alteration at the position corresponding to position 83 is a substitution to N, K or S,

9. The polypeptide of any of embodiments 2 to 8 wherein the alteration at the position corresponding to position 111 is a substitution to D, G, H, R, Q or E.

10. The polypeptide of any of embodiments 5 to 9 wherein the alteration at the position corresponding to position 573 is a substitution to a P, Y, W, H, F, T, I or V.

11. The polypeptide of any of embodiments 5 to 10 wherein the substitution at the position corresponding to position 573 is to a P, Y or W.

12. The polypeptide of any of embodiments 5 to 11 to wherein the substitution at the position corresponding to position 573 is to a P.

13. The polypeptide of any of embodiments 1 to 12 wherein the reference albumin is HSA (SEQ ID No: 2) or a fragment thereof, or a fusion polypeptide comprising HSA or a fragment thereof, most preferably SEQ ID NO: 2.

14. The polypeptide according to any of embodiments 1 to 13, having a stronger binding affinity to FcRn and/or longer plasma half-life than a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof.

15. The polypeptide according any of embodiments 1 to 14, wherein the sequence identity of the polypeptide to SEQ ID NO: 2 is more than 80%, preferably more than 90%, more preferred more than 95%, more preferred more than 96%, even more preferred more than 97%, more preferred more than 98% and most preferred more than 99%.

16. A fusion polypeptide comprising a polypeptide according to any of embodiments 1 to 15 and a fusion partner polypeptide selected from a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

17. A method for preparing a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof having a binding affinity to FcRn which is altered compared to the binding affinity of a reference albumin, fragment or fusion thereof to FcRn, comprising:

(a) Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
(b) Modifying the nucleic acid sequence of step (a), to encode a polypeptide which is a variant albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof comprising:

i. alterations at positions corresponding to one or more (several) positions in Domain I of the parent albumin and one or more (several) positions in Domain III; or

ii. alterations at positions corresponding to one or more of any of positions 78 to 120 of Domain I of SEQ ID NO: 2 or at positions corresponding to one or more (several) of any of positions 425, 505, 510, 512, 524, 527, 531, 534, 569, 573, 575 of Domain III of SEQ ID NO: 2;

(c) optionally introducing the modified sequence of step (b) in a suitable host cell;

(d) optionally growing the cells in a suitable growth medium under condition leading to expression of the polypeptide; and

(e) optionally recovering the polypeptide from the growth medium;

(f) wherein the polypeptide has an altered binding affinity to FcRn and/or an altered plasma half-life compared with the half-life of a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof.

18. The method according to embodiment 17 wherein the one or more (several) alterations in Domain I are selected from positions corresponding to positions from any of 78 to 88 and/or from any of 105 to 120 of SEQ ID NO: 2.

19. The method according to embodiment 17 or 18 wherein the polypeptide comprises alterations corresponding to positions (a) 111 and 573; (b) 82 and 83; (c) 82 and 111; (d) 82 and 112; (e) 82 and 573; (f) 83 and 111; (g) 83 and 112; (h) 83 and 573; (i) 111 and 112; (j) 83, 111, and 573; (k) 112, and 573; (l) 82, 83, and 111; (m) 82, 83, and 112; (n) 82, 83, and 573; (o) 82, 111, and 112; (p) 82, 111, and 573; (q) 82, 112, and 573; (r) 83, 111, and 112; (s) 83, 112, and 573; (t) 111, 112, and 573; (u) 82, 83, 111, and 112; (v) 82, 83, 111, and 573; (w) 82, 83, 112, and 573; (x) 82, 111, 112, and 573; (y) 83, 111, 112, and 573; or (z) 82, 83, 111, 112, and 573 of SEQ ID NO: 2.

20. The method according to any of embodiments 17 to 19 wherein the one or more (several) alterations in Domain I are selected from positions corresponding to 83 and/or 111 of SEQ ID NO: 2.

21. The method according to any of embodiments 17 to 20 wherein the alteration in Domain III is at a position corresponding to 573 of SEQ ID NO: 2.

22. The polypeptide according to any of embodiments 17 to 21 wherein the alteration in Domain I and/or the alteration in Domain III is a substitution.

23. The polypeptide of any of embodiments 20 to 22 wherein the alteration at the position corresponding to position 83 is a substitution to N, K or S,

24. The polypeptide of any of embodiments 20 to 23 wherein the alteration at the position corresponding to position 111 is a substitution to E, Q, D, G, or H.

25. The polypeptide of any of embodiments 20 to 24 wherein the alteration at the position corresponding to position 573 is a substitution to a P, Y, W, H, F, T, I or V.

26. The polypeptide of any of embodiments 20 to 25 wherein the substitution at the position corresponding to position 573 is to a P, Y or W.

27. The polypeptide of any of embodiments 20 to 26 to wherein the substitution at the position corresponding to position 573 is to a P.

28. The method according to any of embodiments 17 to 27 wherein the reference albumin is HSA (SEQ ID No: 2) or a fragment thereof, or a fusion polypeptide comprising HSA or a fragment thereof, most preferably SEQ ID NO: 2.

29. A conjugate comprising a polypeptide according to any of embodiments 1 to 16 or obtainable by a method according to any of embodiments 17 to 28 and a conjugation partner.

30. The conjugate according to embodiment 29 wherein the conjugation partner is a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

31. An associate comprising a polypeptide according to any of embodiments 1 to 16 or obtainable by a method according to any of embodiments 17 to 28 and a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

32. A nanoparticle or microparticle comprising a polypeptide according to any of embodiments 1 to 16 or obtainable by a method according to any of embodiments 17 to 28, a conjugate according to embodiment 29 or 30 or an associate according to embodiment 31.

33. A composition comprising a polypeptide according to any of embodiments 1 to 16 or obtainable by a method according to any of embodiments 17 to 28, a conjugate according to embodiment 29 or 30, an associate according to embodiment 31 or a nanoparticle or microparticle according embodiment 32, wherein the binding affinity of the polypeptide, fusion polypeptide, conjugate, associate or nanoparticle or microparticle to FcRn is stronger than the binding affinity of a composition comprising the corresponding parent albumin, reference albumin, fragment thereof or fusion polypeptide, conjugate, associate or nanoparticle or microparticle comprising said parent albumin, reference albumin or fragment or fusion thereof to FcRn.

34. A composition according to embodiment 33 where the binding affinity of the polypeptide, fusion polypeptide, conjugate, associate or nanoparticle or microparticle to FcRn is stronger than the binding affinity of HSA to FcRn.

35. A composition according to embodiment 33 or 34, wherein the binding coefficient of the variant of to the polypeptide, fusion polypeptide, conjugate, associate or nanoparticle or microparticle to FcRn is less than 0.9X KD of HSA to FcRn, more preferred less than 0.5X KD of HSA to FcRn, more preferred less than 0.1X KD of HSA to FcRn, even more preferred less than 0.05X KD of HSA to FcRn, even more preferred less than 0.02X KD of HSA to FcRn and most preferred less than 0.01X KD of HSA to FcRn.

36. The composition according to any of embodiments 29 to 35, comprising a polypeptide according to any of embodiments 1 to 16 or obtainable by a method according to any of embodiments 17 to 28, a conjugate according to embodiment 29 or 30, an associate according to embodiment 31 or a nanoparticle or microparticle according embodiment 32, further comprising a compound comprising an antibody binding domain (ABD) and a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

37. The composition according to any of embodiments 33 to 36, comprising a pharmaceutically acceptable carrier or excipient.

38. Use of a polypeptide according to any of embodiments 1 to 16 or obtainable by a method according to any of embodiments 17 to 28, a conjugate according to embodiment 29 or 30, an associate according to embodiment 31 or a nanoparticle or microparticle according embodiment 32 or a composition according to any of embodiments 33

to 37 to alter the binding affinity to FcRn or half-life, preferably in plasma, of a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

39. The use according to embodiment 38 wherein the binding affinity to FcRn is increased relative to the binding affinity of a reference comprising or consisting of HSA (SEQ ID NO: 2) or a fragment, fusion, conjugate, associate, nanoparticle or microparticle thereof to FcRn.

40. The use according to embodiment 39 wherein the binding affinity to FcRn is decreased relative to the binding affinity of a reference comprising or consisting of HSA (SEQ ID NO: 2) or a fragment, fusion, conjugate, associate, nanoparticle or microparticle thereof to FcRn.

41. A method for altering the binding affinity to FcRn or half-life preferably in plasma, of a molecule comprising:

(a) where the molecule is a polypeptide, fusing or conjugating the molecule to a polypeptide according to any of embodiments 1 to 16 or obtainable by a method of embodiments 17 to 28, or to a conjugate according to embodiment 29 or 30; associating the molecule to a polypeptide according to any of embodiments 1 to 16 or obtainable by a method of embodiments 17 to 28 or to a conjugate according to embodiment 29 or 30; incorporating the molecule in an associate according to embodiment 31, in nanoparticle or microparticle according to embodiment 32 or a composition according to any of embodiments 33 to 37;

(b) where the molecule is not a polypeptide, conjugating the molecule to a polypeptide according to any of embodiments 1 to 16 or obtainable by a method of embodiments 17 to 28, or to a conjugate according to embodiment 29 or 30; associating the molecule to a polypeptide according to any of embodiments 1 to 16 or obtainable by a method of embodiments 17 to 28 or to a conjugate according to embodiment 29 or 30; incorporating the molecule in an associate according to embodiment 31, in nanoparticle or microparticle according to embodiment 32 or a composition according to any of embodiments 33 to 37.

42. A method according to embodiment 41 wherein the molecule is a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

43. A polypeptide, fusion polypeptide, conjugate, associate, nanoparticle or microparticle or composition thereof according to any of embodiments 1 to 16, 29 to 42 or obtainable by the method of embodiments 17 to 28 wherein the polypeptide, fusion polypeptide, conjugate, associate, nanoparticle or microparticle or composition comprises one or more (several) moiety selected from those described herein.

44. A nucleic acid encoding the polypeptide or fusion polypeptide of any of embodiments 1 to 16.

45. A vector comprising a nucleic acid according to embodiment 44.

46. A host cell comprising a nucleic acid according to embodiment 45 or a vector according to embodiment 34.

47. A host cell according to embodiment 46 wherein the host cell is a eukaryote, preferably a yeast (such as *Saccharomyces cerevisiae*) or a mammalian cell (such as CHO or HEK) or a plant cell (such as rice).

48. A method of prophylaxis, treatment or diagnosis comprising administering a polypeptide, fusion polypeptide, conjugate, composition, associate, nanoparticle or microparticle or polynucleotide according to any of embodiments 1 to 16, 29 to 47 or obtainable by the method of any of embodiments 17 to 28 to a subject.

[0248] The invention is further described by the following examples that should not be construed as limiting the scope of the invention.

Examples

Example 1: Preparation of HSA mutein expression plasmids.

[0249] HSA variants were expressed using standard molecular biology techniques, such as described in Sambrook, J. and D.W. Russell, 2001 (Molecular Cloning: a laboratory manual, 3rd ed. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y).

[0250] Construction of the K573P expression plasmid is described in WO2011/051489 (incorporated herein by refer-

ence). Construction of the remaining expression plasmids was performed as described in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference). Variants HSA T83K, HSA E82A, HSA E82D, HSA P110G, HSA L112F and HSA T83N/N111E were produced as described in Example 6, Method 2 of WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference). Combination mutants containing the K573P substitution were produced as described in "Production of combination mutants with K573P" (WO 2012/150319 (PCT/EP12/058206)), where the required fragments were inserted into appropriately digested pDB4852 (described in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference)). Fragments containing T83N/N111E, T83K, E82A, E82D, P110G and L112F were removed from synthetic constructs *via* the indicated restriction sites (Table 1). The fragment containing the T83N substitution was removed from pDB4874 (described in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference)). Ligation of the polynucleotides encoding HSA variants and plasmids pDB3964/pDB4852 produced plasmids, which were used to express the desired mutants (Table 1). All plasmids were sequenced to confirm that the HSA sequence was only mutated at the desired position(s).

[0251] Construction of HSA T83N, HSA N111E and HSA N111E/K573P was as described in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference).

[0252] Transformation of *S. cerevisiae* was performed as described in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference), employing the 24 hour stocking method described in WO 2011/051489, with the exception that the host strain was *S. cerevisiae* DYB7 (Payne et al (2008) Applied and Environmental Microbiology Vol. 74(24): 7759-7766) with four copies of PDI integrated into the genome.

Table 1: Construction of HSA mutein expression plasmids.

Variant	Restriction enzymes	Digested fragment size (kb)	Plasmid	SEQ ID NO
HSA T83N/N111E	SacII/NheI	0.395	pDB4966	32
HSA T83N/N111 E/K573P	SacII/NheI	0.395	pDB4967	33
HSA T83N/K573P	SacII/NheI	0.395	pDB4968	34
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HSA E82A	SacII/NheI	0.395	pDB4904	36
HSAL112F	SacII/NheI	0.395	pDB4907	37
HSA T83K/K573P	SacII/NheI	0.395	pDB4908	38
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HSA P110G/K573P	SacII/NheI	0.395	pDB4911	44

Example 2: SPR analysis of binding affinity of albumin variants to FcRn

[0253] SPR analyses were performed as described in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference).

[0254] The variants were albumin (SEQ ID NO: 2), each with one point mutation selected from: D108A, N111D, N111G, N111H, N111K, K190A, R197A, K276N, R410A, Y411A, P416A, E425A, E425K, K466A, D471A, R472A, N503D, N503K, E505K, E505Q, H510D, H510E, D512A, D512E, K524A, K525A, T527A, T527D, T527M, E531A, E531H, K534V, H535F, E565V, A569L, A569S, A569V, and V576F.

[0255] Firstly, the variants were analyzed by SPR to determine their binding response (RU) to shFcRn. Only variants showing a binding response more than 20% higher or lower than the binding response of wild-type albumin were analyzed to identify the KD (Table 2, below). Wild-type HSA and HSA with mutation K573P were used as controls.

Table 2: Binding affinity of albumin variants to shFcRn

Molecule	SEQ ID NO:	Ka (10 ³ /Ms)	Kd (10 ⁻³ /s)	KD (μM)
WT rHSA	2	-	-	3.1 ± 0.4*

(continued)

Molecule	SEQ ID NO:	Ka (10 ³ /Ms)	Kd (10 ⁻³ /s)	KD (μM)
HSA K573P	3	-	-	0.4± 0.1*
HSA E505Q	45	2.1	2.9	1.4
HSA N111D	46	0.8	4.4	5.2
HSA T527M	47	2.7	3.3	1.2
HSA N111G	48	1.6	5.2	3.3
HSA N111H	49	0.5	2.4	5.0
HSA D512E	50	2.7	10.9	4.1
HSA K524A	51	3.3	11.6	3.5
HSA T527A	52	2.6	13.7	5.2
HSA E531H	53	3.5	20.8	6.2
HSA N111K	54	0.5	8.3	17.3
HSA E425K	55	3.6	12.4	3.5
HSA K534V	56	4.8	5.5	1.1
HSA H510D	57	0.2	0.4	0.2
HSA A569S	58	0.7	4.8	6.8
HSA D108A	59	0.9	12.7	13.7
*Mean of five repeats, therefore Ka and Kd data are not provided				

[0256] Variants with a lower KD than wild-type HSA have a higher binding affinity to shFcRn. Conversely, variants with a higher KD than wild-type HSA have a lower binding affinity to shFcRn.

[0257] The data for positions 108 and 111 support the involvement of a loop including positions 105 to 120 in interaction with FcRn and therefore that alteration at any position within this loop will modulate the binding affinity of albumin to FcRn.

Example 3. SPR analysis of binding affinity of albumin variants to FcRn

[0258] The variants were albumin (SEQ ID NO: 2), each with one point mutation selected from: N111D, N111G, N111H, N111D/K573P, N111G/K573P, N111H/K573P, E505Q, E425A, T527M, E505Q/K573P, E425A/K573P and T527M/K573P were prepared as described in above.

Table 3: Binding affinity of albumin variants to shFcRn-HIS

Molecule	SEQ ID NO:	Ka (10 ³ /Ms)		Kd (10 ⁻³ /s)		KD (μM)	
WT rHSA	2	-		-		3.6±0.54*	
HSA K573P	3	-		-		0.6±0.12**	
HSA N111D	46	9.8	9.1	17.9	17.9	1.8	2.0
HSA N111G	48	7.4	7.4	20.5	19.2	2.7	2.6
HSA N111H	49	4.4	4.0	15.6	14.2	3.5	3.6
HSA N111D/K573P	60	4.0	4.2	1.9	2.2	0.5	0.5
HSA N111G/K573P	61	4.1	4.7	1.7	2.3	0.4	0.5
HSA N111H/K573P	62	2.9	3.0	1.7	2.2	0.6	0.7
HSA E505Q	45	5.1	5.0	4.9	6.0	1.0	1.2
HSA E425A	63	6.6	7.9	34.1	28.1	5.1	3.6

(continued)

Molecule	SEQ ID NO:	Ka (10 ³ /Ms)		Kd (10 ⁻³ /s)		KD (μM)	
HSA T527M	47	4.9	4.8	4.4	5.1	0.9	1.1
HSA E425A/K573P	64	3.4	3.6	2.5	3.2	0.7	0.9
HSA E505Q/K573P	65	0.4	0.4	0.5	1.1	1.6	2.5
HSA T527M/K573P	66	2.6	2.8	1.2	2.2	0.5	0.8
* Mean of 8 and standard deviation ** Mean of 5 and standard deviation.							

Variants with a lower KD than wild-type HSA have a higher binding affinity to shFcRn. Conversely, variants with a higher KD than wild-type HSA have a lower binding affinity to shFcRn.

[0259] The data for variants including K573P generate increases in affinity consistent with the K573P substitution only.

Example 4. SPR analysis of binding affinity of albumin variants to FcRn

[0260] The variants were albumin (SEQ ID NO: 2), each with one point mutation selected from: N111R, N111Q, N111E, N111R/K573P, N111Q/K573P, N111E/K573P, N109D, N109E, N109Q, N109R, N109K, N109H, N109G, D108E, T83N, L575F and K534V/K573P were prepared as described above.

Table 4a: Binding affinity of albumin variants to shFcRn-HIS

Molecule	SEQ ID NO:	Ka (10 ³ /Ms)		Kd (10 ⁻³ /s)		KD (μM)	
WT HSA	2	-		-		2.0±0.3*	
HSA K573P	3	-		-		0.3±0.0**	
HSAN111E	67	15.3	14.3	13.1	15.2	0.8	1.1
HSA N111E/K573P	68	4.2	-	2.4	-	0.6	-
HSA N109K	69	9.7	6.3	18.3	21.6	1.9	3.4
HSA D108E	70	13.9	7.5	16.6	19.5	1.2	2.6
HSA T83N	71	17.7	15.2	15.6	16.8	0.9	1.1
HSA L575F	72	11.8	8.3	31.3	32.2	2.7	4.0
HSA K534V/K573P	73	4.7	4.5	6.9	6.9	1.5	1.5
* Mean of 11 and standard deviation ** Mean of 5 and standard deviation.							

Table 4b

Molecule	SEQ ID NO:	Ka (10 ³ /Ms)		Kd (10 ⁻³ /s)		KD (μM)	
WT rHSA	2	-		-		3.6±0.54*	
HSA K573P	3	-		-		0.6±0.12**	
HSA N111D	46	9.8	9.1	17.9	17.9	1.8	2.0
HSA N111G	48	7.4	7.4	20.5	19.2	2.7	2.6
HSA N111H	49	4.4	4.0	15.6	14.2	3.5	3.6
* Mean of 8 and standard deviation ** Mean of 5 and standard deviation.							

[0261] The data demonstrate a role for the 108 to 111 loop in binding of HSA to FcRn, with reduced binding affinity observed in the D108A and N111K variants (Table 2). Additional mutations at position 111 demonstrated a range of binding affinities, from the reduced affinity observed for the N111K variant through to the N111E variant, which displayed an increased affinity for FcRn as compared to WT HSA (Table 4). Variant N111Q/K573P (Figure 5, SEQ ID NO: 74)

shows a binding curve with increased response compared to wt HSA and slower dissociation compared to wt HSA, this is consistent with the K573P substitution. The relative position of loop region 108 to 112 of HSA and FcRn (Figure 6) suggests that this region has potential to contribute to FcRn binding as predicted in Example 2. Further details regarding Figures 5 and 6 are provided in WO 2012/150319 (PCT/EP12/058206, incorporated herein by reference).

[0262] The relative position of adjacent loop region of Domain I (domain 1), comprising residues 78 to 88 (Figure 6), suggests that this region has potential to contribute to FcRn binding. This is supported by the observation that the T83N variant shows increased affinity for FcRn compared to WT HSA (Table 4).

[0263] Mutation of the adjacent residues, particularly E82, P110 and L112 (Figure 6), would be predicted to alter the binding affinity of HSA for FcRn.

Example 5: SPR analysis of binding affinity of albumin variants to FcRn

[0264] SPR analyses were performed on a Biacore 3000 instrument (GE Healthcare). Immobilization was carried out on CM5 chips coupled with shFcRn (GeneArt 1177525) using GE Healthcare amine coupling chemistry as per manufacturer's instructions. Immobilized levels of shFcRn-HIS (shFcRn with a 6-His tail on the C-terminus of beta-2-microglobulin) were -1200RU and achieved by injecting 20 μ g/mL shFcRn in sodium acetate pH4.5 (G E Healthcare). Chip surface was left to stabilize with a constant flow (5 μ L/min) of running buffer - Di-basic/Mono-basic phosphate buffer pH5.5 at 25 °C overnight. After ligand stabilization, the chip surface was conditioned by injecting 3 x 45 μ L Di-basic/Mono-basic phosphate buffer at 30 μ L/min followed by HBS_EP (0.01 M HEPES, 0.15 M NaCl, 3mM EDTA, 0.005% surfactant P20) at pH 7.4 (GE Healthcare)) regeneration steps (12s) in between each injection. Surfaces were then checked for activity by injecting 3x45 μ L positive control at 30 μ L/min, followed by 12s regeneration pulse.

[0265] pH 5.5 Binding Analysis: Sensorgrams for binding data were obtained by injecting 45 μ L of 20 μ M (diluted in pH 5.5 buffer) of analytes in pH 5.5 running buffer at 30 μ L/min in duplicate. 2 x 12s regeneration pulses post injection were performed to restore the baseline (HBS-EP pH 7.4; 10 μ L at 50 μ L/min). The reference was then subtracted and BiaEvaluation software 4.1 used to obtain binding analysis data.

[0266] pH 5.5 Kinetic Analysis: Sensorgrams for kinetic data were obtained by injecting 45 μ L of five concentrations: 20 μ M, 4 μ M, 0.8 μ M 0.16 μ M and 0.032 μ M of analytes in pH 5.5 running buffer at 30 μ L/min with a 90s delay post injection (to allow smooth dissociation for kinetic modelling). 2 x 12s regeneration pulses post injection were performed to restore the baseline (HBS-EP pH 7.4; 10 μ L at 50 μ L/min). Analysis was performed on two separate occasions. The reference cell value was then subtracted and Biaevaluation software 4.1 used to obtain kinetic data and confirm KD values.

[0267] SPR was used to identify the binding response of variants to FcRn, the results are shown in Tables 5a and 5b.

Table 5a:

Molecule	SEQ ID NO	Binding Response (RU)
WT rHSA	2	229
HSA K573P	3	300
HSA T83K	35	194
HSA T83K/K573P	38	285
HSA E82A	36	221
HSA E82A/K573P	39	275
HSA E82D	41	227
HSA E82D/K573P	43	269
HSA P110G	42	235
HSA P110G/K573P	44	284
HSA L112F	37	253
HSA L112F/K573P	40	290
Values shown are a mean of two runs.		

Table 5b:

Molecule	SEQ ID NO	Binding Response (RU)
WT rHSA	2	148
HSA K573P	3	181
HSA T83N/N111 E	32	167
Values shown are a mean of two runs.		

[0268] KD analysis was performed on variants to assess variant-FcRn binding affinity relative to HSA-K573-FcRn binding affinity. The results are shown in Table 6. Further analysis was carried out to calculate binding affinities (Table 7).

Table 6:

Molecule	SEQ ID NO:	KD (μ M)	Binding affinity (fold difference, relative to HSA wild-type)
WT rHSA	2	3.82	-
HSAL112F	37	1.44	2.7
HSA T83K	35	1.42	2.7
HSA E82A	36	2.81	1.4
HSA K573P	3	0.18	21.2
HSA L112F/K573P	40	0.108	35.4
HSA T83K/K573P	38	0.147	26.0
HSA E82A/K573P	39	0.174	22.0

Table 7

Molecule	SEQ ID NO:	Ka (1/Ms)	Kd (1/s)	KD (μ M)	Mean KD (μ M)	Fold difference compared to HSA wild-type
WT rHSA	2	0.63×10^4	0.0133	2.11	1.97	-
		0.78×10^4	0.0141	1.83		
HSA K573P	3	0.81×10^4	1.32×10^{-3}	0.162	0.20	9.9
		0.74×10^4	1.77×10^{-3}	0.238		
HSA T83N/N111E/K573P	33	2.28×10^4	1.16×10^{-3}	0.051	0.061	32.3
		2.28×10^4	1.59×10^{-3}	0.070		
HSA T83N/K573P	34	1.55×10^4	1.3×10^{-3}	0.084	0.12	16.4
		1.22×10^4	1.84×10^{-3}	0.15		

[0269] The data show that HSA T83N/N111E/K573P and HSA T83N/K573P have high FcRn binding affinities relative to wild-type HSA. HSA E82A and HSA L112F both show improved binding to FcRn compared to wild-type HSA binding to FcRn and this suggests that the loops comprising amino acids 78 to 88 of HSA (SEQ ID NO: 2) and 105 to 120 of HSA (SEQ ID NO: 2) are involved in the binding of HSA to FcRn.

[0270] HSA with single mutations at position L112 or T83 show similar FcRn binding affinities to each other. However, the double mutation of L112 and K573 has a stronger binding affinity to FcRn than the double mutation of T83 and K573.

Table 8

Molecule	SEQ ID NO:	Ka (10 ³ /MS)	Kd (10 ³ /s)	KD (μM)	Mean KD (μM)
WT HSA	2	4.3	63.6	13.7	13.8
		5.6	77.6	13.9	
HSA-K573P	3	4.3	6.2	1.4	1.1
		5.2	4.6	0.89	
HSA-E82D	41	2.3	84.3	36.9	24.1
		6.5	73.0	11.3	
HSA-E82D/K573P	43	4.9	6.7	1.4	1.1
		5.5	5.0	0.9	

[0271] The data of Table 8 show that HSA-E82D has a low FcRn binding affinity relative to wild-type albumin and HSA-K573P has a high FcRn binding relative to wild-type albumin. However, the double mutant HSA-E82D/K573P shows the same FcRn binding affinity as HSA-K573P, i.e. inclusion of the E82D substitution does not adversely affect FcRn binding.

[0272] The invention described and claimed herein is not to be limited in scope by the specific aspects herein disclosed, since these aspects are intended as illustrations of several aspects of the invention. Any equivalent aspects are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. In the case of conflict, the present disclosure including definitions will control.

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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25 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

30 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

35 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

40 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

45 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

50 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

55 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

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	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	180	185	190	
5	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	195	200	205	
10	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	210	215	220	
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	225	230	235	240
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	245	250	255	
20	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	260	265	270	
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	275	280	285	
25	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	290	295	300	
30	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	305	310	315	320
35	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	325	330	335	
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	340	345	350	
40	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	355	360	365	
45	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	370	375	380	
50	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	385	390	395	400
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	405	410	415	
55	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	420	425	430	

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	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
5	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
10	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
15	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
					485					490					495		
20	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
25	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
30	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
	530						535					540					
35	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
40	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
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45	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu								
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60	Tyr	Ser	Arg	Gly	Val	Phe	Arg	Arg	Asp	Ala	His	Lys	Ser	Glu	Val	Ala	
				20					25					30			
65	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	
			35					40					45				
70	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	
	50						55					60					

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	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	65	70	75	80
5	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	85	90	95	
10	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	100	105	110	
	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	115	120	125	
15	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	130	135	140	
20	Asp	Val	Met	Cys	Thr	Ala	Phe	His	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	145	150	155	160
	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	165	170	175	
25	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	180	185	190	
30	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	195	200	205	
35	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	210	215	220	
	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	225	230	235	240
40	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	245	250	255	
45	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Thr	Glu	Cys	Cys	His	Gly	260	265	270	
	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	275	280	285	
50	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	290	295	300	
55	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	305	310	315	320

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	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	
					325					330					335		
5	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	
				340					345					350			
10	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	
			355					360					365				
15	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	
		370					375					380					
20	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	
	385					390					395					400	
25	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	
					405					410					415		
30	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	
				420				425						430			
35	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	
			435					440					445				
40	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	
		450					455					460					
45	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	
	465					470					475					480	
50	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	
					485					490					495		
55	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	
				500					505					510			
60	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	
			515					520					525				
65	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	
		530					535					540					
70	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	
	545					550					555					560	
75	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	

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565

570

575

5

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
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Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu

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Ser Val Leu Asp Ser Gly His Ser Ser Ser Ala Tyr Ser Arg Gly
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Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
35 40 45

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Val Ala Phe Ala
50 55 60

35

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
65 70 75 80

40

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
85 90 95

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
100 105 110

45

Val Ala Thr Leu Arg Glu Lys Tyr Gly Glu Met Ala Asp Cys Cys Ala
115 120 125

50

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
130 135 140

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
145 150 155 160

55

Thr Ala Phe His Asp Asn Glu Gly Thr Phe Leu Lys Lys Tyr Leu Tyr

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	165					170					175					
5	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe
				180					185					190		
10	Phe	Ala	Glu	Arg	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala
			195					200					205			
15	Asp	Lys	Ala	Ala	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu
		210					215					220				
20	Gly	Lys	Ala	Ser	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln
	225					230					235					240
25	Lys	Phe	Gly	Glu	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser
					245					250					255	
30	Gln	Arg	Phe	Pro	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr
				260					265					270		
35	Asp	Leu	Thr	Lys	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu
			275					280					285			
40	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln
		290					295					300				
45	Asp	Ser	Ile	Ser	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu
	305					310					315					320
50	Glu	Lys	Ser	His	Cys	Leu	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala
					325					330					335	
55	Asp	Leu	Pro	Ser	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Glu	Val	Cys
				340				345						350		
60	Lys	Asn	Tyr	Ala	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr
			355					360					365			
65	Glu	Tyr	Ala	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg
		370					375					380				
70	Leu	Ala	Lys	Thr	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala
	385					390					395					400
75	Asp	Pro	His	Glu	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu
					405					410					415	

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	Val	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	
				420					425					430			
5	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	
			435					440					445				
10	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	
		450					455					460					
15	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	
	465					470					475					480	
20	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	
					485					490					495		
25	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	
				500					505					510			
30	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	
			515					520					525				
35	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	
		530					535					540					
40	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	
	545					550					555					560	
45	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	
					565					570					575		
50	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	
				580					585					590			
55	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	
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	Tyr	Ser	Arg	Gly	Val	Phe	Arg	Arg	Asp	Thr	His	Lys	Ser	Glu	Val	Ala	
				20					25					30			
5	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	Glu	His	Phe	Lys	Gly	Leu	Val	Leu	
			35				40						45				
10	Val	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Glu	Glu	His	Val	
		50					55					60					
15	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	
	65					70					75					80	
20	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	
					85					90					95		
25	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	
				100					105					110			
30	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	
			115					120					125				
35	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	Pro	Pro	Leu	Val	Arg	Pro	Glu	Val	
		130					135					140					
40	Asp	Val	Met	Cys	Thr	Ala	Phe	His	Asp	Asn	Glu	Ala	Thr	Phe	Leu	Lys	
	145					150					155					160	
45	Lys	Tyr	Leu	Tyr	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	
					165					170					175		
50	Glu	Leu	Leu	Phe	Phe	Ala	Ala	Arg	Tyr	Lys	Ala	Ala	Phe	Ala	Glu	Cys	
				180					185					190			
55	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	
			195					200					205				
60	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	
		210					215					220					
65	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Asp	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	
	225					230					235					240	
70	Ala	Arg	Leu	Ser	Gln	Lys	Phe	Pro	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	
					245					250					255		
75	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Thr	Glu	Cys	Cys	His	Gly	
				260					265					270			

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	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Met	
		275						280					285				
5	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Asp	
		290					295					300					
	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	Cys	Leu	Ala	Glu	Val	Glu	Asn	Asp	
10		305				310					315					320	
	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	Leu	Ala	Ala	Asp	Tyr	Val	Glu	Ser	
					325					330					335		
15	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	
				340					345					350			
	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Met	
20			355					360					365				
	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Ala	Tyr	Glu	Ala	Thr	Leu	Glu	Lys	Cys	
25		370					375					380					
	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	
		385				390					395					400	
30	Phe	Gln	Pro	Leu	Val	Glu	Glu	Pro	Gln	Asn	Leu	Val	Lys	Gln	Asn	Cys	
				405						410					415		
	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	
35				420					425					430			
	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	
			435					440					445				
40	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	Val	Gly	Ala	Lys	Cys	Cys	Lys	Leu	
		450					455					460					
	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	
45						470					475					480	
	Leu	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Lys	
50					485					490					495		
	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	
				500					505					510			
55	Ser	Ala	Leu	Glu	Leu	Asp	Glu	Ala	Tyr	Val	Pro	Lys	Ala	Phe	Asn	Ala	
			515					520					525				

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	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	Met	Cys	Thr	Leu	Ser	Glu	Lys	Glu	
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5	Lys	Gln	Val	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	
	545					550					555					560	
	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	Lys	Gly	Val	Met	Asp	Asn	Phe	Ala	
10					565					570					575		
	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Ala	Cys	Phe	
				580					585					590			
15	Ala	Glu	Glu	Gly	Pro	Lys	Phe	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Ala	
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30	Phe	Ser	Arg	Gly	Leu	Phe	Arg	Arg	Asp	Ala	His	Lys	Ser	Glu	Ile	Ala	
				20					25					30			
	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	Gln	His	Phe	Lys	Gly	Leu	Val	Leu	
35			35					40					45				
	Ile	Ala	Phe	Ser	Gln	Phe	Leu	Gln	Lys	Cys	Pro	Tyr	Glu	Glu	His	Val	
		50					55					60					
40	Lys	Leu	Val	Asn	Glu	Val	Thr	Asp	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	
	65					70					75					80	
	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	
45					85					90					95		
	Lys	Leu	Cys	Ala	Ile	Pro	Thr	Leu	Arg	Asp	Ser	Tyr	Gly	Glu	Leu	Ala	
50				100					105					110			
	Asp	Cys	Cys	Ala	Lys	Lys	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Lys	
				115				120					125				
55	His	Lys	Asp	Asp	His	Pro	Asn	Leu	Pro	Pro	Phe	Val	Arg	Pro	Asp	Ala	
		130					135					140					

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	Glu	Ala	Met	Cys	Thr	Ser	Phe	Gln	Glu	Asn	Ala	Val	Thr	Phe	Met	Gly	145	150	155				160
5	His	Tyr	Leu	His	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro		165	170				175
10	Glu	Leu	Leu	Tyr	Tyr	Ala	Glu	Lys	Tyr	Ser	Ala	Ile	Met	Thr	Glu	Cys		180	185				190
	Cys	Gly	Glu	Ala	Asp	Lys	Ala	Ala	Cys	Ile	Thr	Pro	Lys	Leu	Asp	Ala		195	200				205
15	Leu	Lys	Glu	Lys	Ala	Leu	Ala	Ser	Ser	Val	Asn	Gln	Arg	Leu	Lys	Cys		210	215				220
20	Ser	Ser	Leu	Gln	Arg	Phe	Gly	Gln	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	225	230	235				240
25	Ala	Arg	Met	Ser	Gln	Lys	Phe	Pro	Lys	Ala	Asp	Phe	Ala	Glu	Ile	Thr		245	250				255
	Lys	Leu	Ala	Thr	Asp	Leu	Thr	Lys	Leu	Thr	Glu	Glu	Cys	Cys	His	Gly		260	265				270
30	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Glu	Leu	Ala	Lys	Tyr	Met		275	280				285
35	Cys	Glu	Asn	Gln	Ala	Ser	Ile	Ser	Ser	Lys	Leu	Gln	Ala	Cys	Cys	Asp		290	295				300
40	Lys	Pro	Val	Leu	Lys	Lys	Ser	His	Cys	Leu	Ser	Glu	Val	Glu	Asn	Asp	305	310	315				320
	Asp	Leu	Pro	Ala	Asp	Leu	Pro	Ser	Leu	Ala	Ala	Asp	Phe	Val	Glu	Asp		325	330				335
45	Lys	Glu	Val	Cys	Lys	Asn	Tyr	Ala	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly		340	345				350
50	Thr	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Ala		355	360				365
	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Lys	Tyr	Glu	Ala	Thr	Leu	Glu	Lys	Cys		370	375				380
55	Cys	Ala	Glu	Ala	Asp	Pro	Ser	Ala	Cys	Tyr	Gly	Lys	Val	Leu	Asp	Glu							

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	385		390		395		400									
5	Phe	Gln	Pro	Leu	Val	Glu	Glu	Pro	Lys	Asn	Leu	Val	Lys	Ala	Asn	Cys
				405						410					415	
10	Glu	Leu	Phe	Glu	Lys	Leu	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Leu	Ile
				420					425					430		
15	Val	Arg	Tyr	Thr	Gln	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val
			435					440					445			
20	Glu	Ala	Ala	Arg	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Val	Leu
		450					455					460				
25	Pro	Glu	Ala	Gln	Arg	Leu	Pro	Cys	Val	Glu	Asp	Tyr	Ile	Ser	Ala	Ile
	465					470					475					480
30	Leu	Asn	Arg	Val	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Gln
				485						490					495	
35	Val	Thr	Lys	Cys	Cys	Thr	Gly	Ser	Val	Val	Glu	Arg	Arg	Pro	Cys	Phe
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40	Ser	Ala	Leu	Pro	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Lys	Ala
			515					520					525			
45	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Ser	Leu	Pro	Glu	Lys	Glu
		530					535					540				
50	Lys	Gln	Met	Lys	Lys	Gln	Ala	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys
	545					550					555					560
55	Pro	Lys	Ala	Thr	Gly	Pro	Gln	Leu	Arg	Thr	Val	Leu	Gly	Glu	Phe	Thr
					565					570					575	
60	Ala	Phe	Leu	Asp	Lys	Cys	Cys	Lys	Ala	Glu	Asp	Lys	Glu	Ala	Cys	Phe
			580						585					590		
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5	Tyr	Ser	Arg	Gly 20	Val	Phe	Arg Arg Glu 25	Ala His Lys Ser Glu 30	Ile Ala
10	His	Arg	Phe 35	Asn Asp	Leu	Gly	Glu Gly 40	His Phe Lys Gly 45	Leu Val Leu
15	Ile	Thr	Leu	Ser	Gln	His	Leu Gln Lys Ser Pro Phe 50 55 60	Glu Glu His Val	
20	Lys	Leu	Val	Asn	Glu	Val	Thr Asp Phe Ala Lys Ala Cys Val Ala Asp 65 70 75 80		
25	Glu	Ser	Ala	Gln	Asn	Cys	Gly Lys Ala Ile Ala Thr Leu Phe Gly Asp 85 90 95		
30	Lys	Val	Cys	Ala	Ile	Pro	Ser Leu Arg Glu Thr Tyr Gly Glu Leu Ala 100 105 110		
35	Asp	Cys	Cys	Ala	Lys	Glu	Asp Pro Asp Arg Val Glu Cys Phe Leu Gln 115 120 125		
40	His	Lys	Asp	Asp	Asn	Pro	Asn Leu Pro Pro Phe Glu Arg Pro Glu Pro 130 135 140		
45	Glu	Ala	Leu	Cys	Thr	Ala	Phe Lys Glu Asn Asn Asp Arg Phe Ile Gly 145 150 155 160		
50	His	Tyr	Leu	Tyr	Glu	Val	Ser Arg Arg His Pro Tyr Phe Tyr Ala Pro 165 170 175		
55	Glu	Leu	Leu	Tyr	Tyr	Ala	Glu Lys Tyr Lys Asn Ala Leu Thr Glu Cys 180 185 190		
	Cys	Glu	Ala	Ala	Asp	Lys	Ala Ala Cys Leu Thr Pro Lys Leu Asp Ala 195 200 205		
	Ile	Lys	Glu	Lys	Ala	Leu	Val Ser Ser Ala Gln Gln Arg Leu Lys Cys 210 215 220		
	Ala	Ser	Leu	Gln	Lys	Phe	Gly Glu Arg Ala Phe Lys Ala Trp Ser Val 225 230 235 240		
	Ala	Arg	Leu	Ser	Gln	Lys	Phe Pro Lys Ala Glu Phe Ala Glu Ile Ser 245 250 255		

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	Thr	Ile	Val	Thr	Ser	Leu	Thr	Lys	Val	Thr	Lys	Glu	Cys	Cys	His	Gly	
				260					265						270		
5	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Gln	Glu	Leu	Ala	Lys	Tyr	Met	
			275					280					285				
10	Cys	Glu	His	Gln	Asp	Ser	Ile	Ser	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Val	
		290					295					300					
15	Lys	Pro	Thr	Leu	Gln	Lys	Ala	His	Cys	Ile	Leu	Glu	Ile	Gln	Arg	Asp	
	305					310					315					320	
20	Glu	Leu	Pro	Thr	Glu	Leu	Pro	Asp	Leu	Ala	Val	Asp	Phe	Val	Glu	Asp	
					325					330					335		
25	Lys	Glu	Val	Cys	Lys	Asn	Phe	Ala	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	
				340					345					350			
30	Thr	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Glu	Tyr	Ser	Ile	Gly	
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35	Met	Leu	Leu	Arg	Ile	Ala	Lys	Gly	Tyr	Glu	Ala	Lys	Leu	Glu	Lys	Cys	
	370						375					380					
40	Cys	Ala	Glu	Ala	Asp	Pro	His	Ala	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	
	385					390					395					400	
45	Leu	Gln	Pro	Leu	Ile	Asp	Glu	Pro	Lys	Lys	Leu	Val	Gln	Gln	Asn	Cys	
					405					410					415		
50	Glu	Leu	Phe	Asp	Lys	Leu	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Leu	Ala	
				420					425					430			
55	Val	Arg	Tyr	Thr	Gln	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	
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60	Glu	Tyr	Ala	Arg	Lys	Leu	Gly	Ser	Val	Gly	Thr	Lys	Cys	Cys	Ser	Leu	
	450						455					460					
65	Pro	Glu	Thr	Glu	Arg	Leu	Ser	Cys	Thr	Glu	Asn	Tyr	Leu	Ala	Leu	Ile	
	465					470					475					480	
70	Leu	Asn	Arg	Leu	Cys	Ile	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Arg	
					485					490					495		
75	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	
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	Ser	Ala	Leu	His	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Pro	Phe	His	Ala	
			515					520					525				
5	Asp	Ser	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Pro	Glu	Lys	Glu	
		530					535					540					
10	Lys	Gln	Val	Lys	Lys	Gln	Met	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	
	545					550					555					560	
15	Pro	Lys	Ala	Ser	Glu	Glu	Gln	Met	Lys	Thr	Val	Met	Gly	Asp	Phe	Ala	
					565					570					575		
20	Ala	Phe	Leu	Lys	Lys	Cys	Cys	Asp	Ala	Asp	Asn	Lys	Glu	Ala	Cys	Phe	
				580					585					590			
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35	Phe	Ser	Arg	Gly	Val	Phe	Arg	Arg	Glu	Ala	His	Lys	Ser	Glu	Ile	Ala	
				20					25					30			
40	His	Arg	Tyr	Asn	Asp	Leu	Gly	Glu	Gln	His	Phe	Lys	Gly	Leu	Val	Leu	
			35					40					45				
45	Ile	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	Lys	Cys	Ser	Tyr	Asp	Glu	His	Ala	
		50					55					60					
50	Lys	Leu	Val	Gln	Glu	Val	Thr	Asp	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	
	65					70					75					80	
55	Glu	Ser	Ala	Ala	Asn	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	
					85					90					95		
	Lys	Leu	Cys	Ala	Ile	Pro	Asn	Leu	Arg	Glu	Asn	Tyr	Gly	Glu	Leu	Ala	
				100					105					110			
	Asp	Cys	Cys	Thr	Lys	Gln	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	
			115					120					125				

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	His	Lys	Asp	Asp	Asn	Pro	Ser	Leu	Pro	Pro	Phe	Glu	Arg	Pro	Glu	Ala	
	130						135					140					
5	Glu	Ala	Met	Cys	Thr	Ser	Phe	Lys	Glu	Asn	Pro	Thr	Thr	Phe	Met	Gly	
	145					150				155						160	
10	His	Tyr	Leu	His	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	
					165					170					175		
15	Glu	Leu	Leu	Tyr	Tyr	Ala	Glu	Gln	Tyr	Asn	Glu	Ile	Leu	Thr	Gln	Cys	
				180					185					190			
20	Cys	Ala	Glu	Ala	Asp	Lys	Glu	Ser	Cys	Leu	Thr	Pro	Lys	Leu	Asp	Gly	
			195					200					205				
25	Val	Lys	Glu	Lys	Ala	Leu	Val	Ser	Ser	Val	Arg	Gln	Arg	Met	Lys	Cys	
	210						215					220					
30	Ser	Ser	Met	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	
	225					230					235					240	
35	Ala	Arg	Leu	Ser	Gln	Thr	Phe	Pro	Asn	Ala	Asp	Phe	Ala	Glu	Ile	Thr	
					245					250					255		
40	Lys	Leu	Ala	Thr	Asp	Leu	Thr	Lys	Val	Asn	Lys	Glu	Cys	Cys	His	Gly	
				260					265					270			
45	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Glu	Leu	Ala	Lys	Tyr	Met	
			275					280					285				
50	Cys	Glu	Asn	Gln	Ala	Thr	Ile	Ser	Ser	Lys	Leu	Gln	Thr	Cys	Cys	Asp	
	290						295					300					
55	Lys	Pro	Leu	Leu	Lys	Lys	Ala	His	Cys	Leu	Ser	Glu	Val	Glu	His	Asp	
	305					310					315					320	
60	Thr	Met	Pro	Ala	Asp	Leu	Pro	Ala	Ile	Ala	Ala	Asp	Phe	Val	Glu	Asp	
					325					330					335		
65	Gln	Glu	Val	Cys	Lys	Asn	Tyr	Ala	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	
				340					345					350			
70	Thr	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Ser	
			355					360					365				
75	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Lys	Tyr	Glu	Ala	Thr	Leu	Glu	Lys	Cys	
	370						375					380					

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	Cys	Ala	Glu	Ala	Asn	Pro	Pro	Ala	Cys	Tyr	Gly	Thr	Val	Leu	Ala	Glu	385		390	395		400
5	Phe	Gln	Pro	Leu	Val	Glu	Glu	Pro	Lys	Asn	Leu	Val	Lys	Thr	Asn	Cys		405	410		415	
10	Asp	Leu	Tyr	Glu	Lys	Leu	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Ile	Leu		420	425		430	
	Val	Arg	Tyr	Thr	Gln	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val		435	440		445	
15	Glu	Ala	Ala	Arg	Asn	Leu	Gly	Arg	Val	Gly	Thr	Lys	Cys	Cys	Thr	Leu		450	455		460	
20	Pro	Glu	Asp	Gln	Arg	Leu	Pro	Cys	Val	Glu	Asp	Tyr	Leu	Ser	Ala	Ile	465	470	475		480	
25	Leu	Asn	Arg	Val	Cys	Leu	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	His		485	490		495	
	Val	Thr	Lys	Cys	Cys	Ser	Gly	Ser	Leu	Val	Glu	Arg	Arg	Pro	Cys	Phe		500	505		510	
30	Ser	Ala	Leu	Thr	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Lys	Ala		515	520		525	
35	Glu	Thr	Phe	Thr	Phe	His	Ser	Asp	Ile	Cys	Thr	Leu	Pro	Glu	Lys	Glu	530	535		540		
40	Lys	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Ala	Glu	Leu	Val	Lys	His	Lys	545	550	555		560	
	Pro	Lys	Ala	Thr	Ala	Glu	Gln	Leu	Lys	Thr	Val	Met	Asp	Asp	Phe	Ala		565	570		575	
45	Gln	Phe	Leu	Asp	Thr	Cys	Cys	Lys	Ala	Ala	Asp	Lys	Asp	Thr	Cys	Phe		580	585		590	
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Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
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10

His Arg Phe Lys Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu
35 40 45

15

Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Pro Tyr Glu Glu His Ile
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Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
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Glu Asn Ala Glu Asn Cys Asp Lys Ser Ile His Thr Leu Phe Gly Asp
85 90 95

25

Lys Leu Cys Ala Ile Pro Lys Leu Arg Asp Asn Tyr Gly Glu Leu Ala
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Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

30

His Lys Asp Asp Asn Pro Asn Leu Pro Pro Phe Gln Arg Pro Glu Ala
130 135 140

35

Glu Ala Met Cys Thr Ser Phe Gln Glu Asn Pro Thr Ser Phe Leu Gly
145 150 155 160

40

His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Tyr Tyr Ala Glu Lys Tyr Asn Glu Val Leu Thr Gln Cys
180 185 190

45

Cys Thr Glu Ser Asp Lys Ala Ala Cys Leu Thr Pro Lys Leu Asp Ala
195 200 205

50

Val Lys Glu Lys Ala Leu Val Ala Ala Val Arg Gln Arg Met Lys Cys
210 215 220

Ser Ser Met Gln Arg Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

55

Ala Arg Met Ser Gln Arg Phe Pro Asn Ala Glu Phe Ala Glu Ile Thr

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	245	250	255
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20	Lys Pro Val Leu Gln Lys Ser Gln Cys Leu Ala Glu Ile Glu His Asp 305 310 315 320		
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40	Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys 370 375 380		
45	Cys Ala Glu Gly Asp Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu 385 390 395 400		
50	Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys 405 410 415		
55	Glu Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Val Leu 420 425 430		
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65	Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu 450 455 460		
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75	Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys 485 490 495		

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5	Ser	Ala	Leu	Thr	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Lys	Ala	
			515					520					525				
10	Glu	Thr	Phe	Thr	Phe	His	Ser	Asp	Ile	Cys	Thr	Leu	Pro	Asp	Lys	Glu	
		530					535					540					
15	Lys	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Ala	Glu	Leu	Val	Lys	His	Lys	
	545					550					555					560	
20	Pro	Lys	Ala	Thr	Glu	Asp	Gln	Leu	Lys	Thr	Val	Met	Gly	Asp	Phe	Ala	
					565					570					575		
25	Gln	Phe	Val	Asp	Lys	Cys	Cys	Lys	Ala	Ala	Asp	Lys	Asp	Asn	Cys	Phe	
				580					585					590			
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	1				5					10				15			
40	Tyr	Ser	Arg	Gly	Val	Phe	Arg	Arg	Asp	Thr	His	Lys	Ser	Glu	Ile	Ala	
				20					25					30			
45	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	Glu	His	Phe	Lys	Gly	Leu	Val	Leu	
			35					40					45				
50	Ile	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Asp	Glu	His	Val	
		50					55					60					
55	Lys	Leu	Val	Asn	Glu	Leu	Thr	Glu	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	
	65					70					75					80	
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					85					90					95		
	Glu	Leu	Cys	Lys	Val	Ala	Ser	Leu	Arg	Glu	Thr	Tyr	Gly	Asp	Met	Ala	
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		130					135					140					
	Thr	Leu	Cys	Asp	Glu	Phe	Lys	Ala	Asp	Glu	Lys	Lys	Phe	Trp	Gly	Lys	
10		145				150					155					160	
	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	
					165					170					175		
15	Leu	Leu	Tyr	Tyr	Ala	Asn	Lys	Tyr	Asn	Gly	Val	Phe	Gln	Glu	Cys	Cys	
				180					185					190			
	Gln	Ala	Glu	Asp	Lys	Gly	Ala	Cys	Leu	Leu	Pro	Lys	Ile	Glu	Thr	Met	
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	Arg	Glu	Lys	Val	Leu	Ala	Ser	Ser	Ala	Arg	Gln	Arg	Leu	Arg	Cys	Ala	
		210					215					220					
25	Ser	Ile	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Leu	Lys	Ala	Trp	Ser	Val	Ala	
		225				230					235					240	
	Arg	Leu	Ser	Gln	Lys	Phe	Pro	Lys	Ala	Glu	Phe	Val	Glu	Val	Thr	Lys	
30					245					250					255		
	Leu	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	Asp	
35				260					265					270			
	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	
			275					280					285				
40	Asp	Asn	Gln	Asp	Thr	Ile	Ser	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Asp	Lys	
		290					295					300					
	Pro	Leu	Leu	Glu	Lys	Ser	His	Cys	Ile	Ala	Glu	Val	Glu	Lys	Asp	Ala	
45		305				310					315					320	
	Ile	Pro	Glu	Asn	Leu	Pro	Pro	Leu	Thr	Ala	Asp	Phe	Ala	Glu	Asp	Lys	
				325						330					335		
50	Asp	Val	Cys	Lys	Asn	Tyr	Gln	Glu	Ala	Lys	Asp	Ala	Phe	Leu	Gly	Ser	
				340					345					350			
	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Glu	Tyr	Ala	Val	Ser	Val	
55			355					360					365				

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	Leu	Leu	Arg	Leu	Ala	Lys	Glu	Tyr	Glu	Ala	Thr	Leu	Glu	Glu	Cys	Cys	
	370						375					380					
5	Ala	Lys	Asp	Asp	Pro	His	Ala	Cys	Tyr	Ser	Thr	Val	Phe	Asp	Lys	Leu	
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10	Lys	His	Leu	Val	Asp	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Asp	
					405					410					415		
15	Gln	Phe	Glu	Lys	Leu	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Leu	Ile	Val	
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20	Arg	Tyr	Thr	Arg	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	
			435					440					445				
25	Val	Ser	Arg	Ser	Leu	Gly	Lys	Val	Gly	Thr	Arg	Cys	Cys	Thr	Lys	Pro	
	450						455					460					
30	Glu	Ser	Glu	Arg	Met	Pro	Cys	Thr	Glu	Asp	Tyr	Leu	Ser	Leu	Ile	Leu	
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35	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Lys	Val	
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40	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	
				500					505					510			
45	Ala	Leu	Thr	Pro	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Ala	Phe	Asp	Glu	Lys	
			515					520					525				
50	Leu	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Pro	Asp	Thr	Glu	Lys	
	530						535					540					
55	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Leu	Lys	His	Lys	Pro	
	545					550					555					560	
60	Lys	Ala	Thr	Glu	Glu	Gln	Leu	Lys	Thr	Val	Met	Glu	Asn	Phe	Val	Ala	
					565					570					575		
65	Phe	Val	Asp	Lys	Cys	Cys	Ala	Ala	Asp	Asp	Lys	Glu	Ala	Cys	Phe	Ala	
				580					585					590			
70	Val	Glu	Gly	Pro	Lys	Leu	Val	Val	Ser	Thr	Gln	Thr	Ala	Leu	Ala		
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<212> PRT
 <213> Equus caballus
 <400> 12

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15	His	Arg	Phe	Asn	Asp	Leu	Gly	Glu	Lys	His	Phe	Lys	Gly	Leu	Val	Leu	35	40	45	
20	Val	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	50	55	60	
25	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	Phe	Ala	Lys	Lys	Cys	Ala	Ala	Asp	65	70	75	80
30	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	85	90	95	
35	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	Arg	Ala	Thr	Tyr	Gly	Glu	Leu	Ala	100	105	110	
40	Asp	Cys	Cys	Glu	Lys	Gln	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Thr	115	120	125	
45	His	Lys	Asp	Asp	His	Pro	Asn	Leu	Pro	Lys	Leu	Lys	Pro	Glu	Pro	Asp	130	135	140	
50	Ala	Gln	Cys	Ala	Ala	Phe	Gln	Glu	Asp	Pro	Asp	Lys	Phe	Leu	Gly	Lys	145	150	155	160
55	Tyr	Leu	Tyr	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Gly	Pro	Glu	165	170	175	
	Leu	Leu	Phe	His	Ala	Glu	Glu	Tyr	Lys	Ala	Asp	Phe	Thr	Glu	Cys	Cys	180	185	190	
	Pro	Ala	Asp	Asp	Lys	Leu	Ala	Cys	Leu	Ile	Pro	Lys	Leu	Asp	Ala	Leu	195	200	205	
	Lys	Glu	Arg	Ile	Leu	Leu	Ser	Ser	Ala	Lys	Glu	Arg	Leu	Lys	Cys	Ser	210	215	220	
	Ser	Phe	Gln	Asn	Phe	Gly	Glu	Arg	Ala	Val	Lys	Ala	Trp	Ser	Val	Ala	225	230	235	240

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	Arg	Leu	Ser	Gln	Lys	Phe	Pro	Lys	Ala	Asp	Phe	Ala	Glu	Val	Ser	Lys	
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5	Ile	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	Asp	
				260					265					270			
10	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	
			275					280					285				
15	Glu	His	Gln	Asp	Ser	Ile	Ser	Gly	Lys	Leu	Lys	Ala	Cys	Cys	Asp	Lys	
		290					295					300					
20	Pro	Leu	Leu	Gln	Lys	Ser	His	Cys	Ile	Ala	Glu	Val	Lys	Glu	Asp	Asp	
	305					310					315					320	
25	Leu	Pro	Ser	Asp	Leu	Pro	Ala	Leu	Ala	Ala	Asp	Phe	Ala	Glu	Asp	Lys	
					325					330					335		
30	Glu	Ile	Cys	Lys	His	Tyr	Lys	Asp	Ala	Lys	Asp	Val	Phe	Leu	Gly	Thr	
				340					345					350			
35	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Ser	Leu	
			355					360					365				
40	Leu	Leu	Arg	Ile	Ala	Lys	Thr	Tyr	Glu	Ala	Thr	Leu	Glu	Lys	Cys	Cys	
		370					375					380					
45	Ala	Glu	Ala	Asp	Pro	Pro	Ala	Cys	Tyr	Arg	Thr	Val	Phe	Asp	Gln	Phe	
	385					390					395					400	
50	Thr	Pro	Leu	Val	Glu	Glu	Pro	Lys	Ser	Leu	Val	Lys	Lys	Asn	Cys	Asp	
					405					410					415		
55	Leu	Phe	Glu	Glu	Val	Gly	Glu	Tyr	Asp	Phe	Gln	Asn	Ala	Leu	Ile	Val	
				420					425					430			
60	Arg	Tyr	Thr	Lys	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	
			435					440					445				
65	Ile	Gly	Arg	Thr	Leu	Gly	Lys	Val	Gly	Ser	Arg	Cys	Cys	Lys	Leu	Pro	
		450					455					460					
70	Glu	Ser	Glu	Arg	Leu	Pro	Cys	Ser	Glu	Asn	His	Leu	Ala	Leu	Ala	Leu	
	465					470					475					480	
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	485	490	495
5	Thr Lys Cys Cys Thr Asp Ser Leu	Ala Glu Arg Arg Pro Cys Phe Ser	
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10	Ala Leu Glu Leu Asp Glu Gly Tyr Val Pro Lys Glu Phe Lys Ala Glu		
	515	520	525
15	Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Glu Asp Glu Lys		
	530	535	540
20	Gln Ile Lys Lys Gln Ser Ala Leu Ala Glu Leu Val Lys His Lys Pro		
	545	550	555
25	Lys Ala Thr Lys Glu Gln Leu Lys Thr Val Leu Gly Asn Phe Ser Ala		
	565	570	575
30	Phe Val Ala Lys Cys Cys Gly Arg Glu Asp Lys Glu Ala Cys Phe Ala		
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60	His Arg Phe Asn Asp Leu Gly Glu Lys His Phe Lys Gly Leu Val Leu		
	35	40	45
65	Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val		
	50	55	60
70	Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Lys Cys Ala Ala Asp		
	65	70	75
75	Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp		
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80	Lys Leu Cys Thr Val Ala Thr Leu Arg Ala Thr Tyr Gly Glu Leu Ala		

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	100						105						110					
5	Asp	Cys	Cys	Glu	Lys	Gln	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Thr		
			115					120					125					
	His	Lys	Asp	Asp	His	Pro	Asn	Leu	Pro	Lys	Leu	Lys	Pro	Glu	Pro	Asp		
10		130					135					140						
	Ala	Gln	Cys	Ala	Ala	Phe	Gln	Glu	Asp	Pro	Asp	Lys	Phe	Leu	Gly	Lys		
	145					150					155					160		
15	Tyr	Leu	Tyr	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Gly	Pro	Glu		
					165					170					175			
	Leu	Leu	Phe	His	Ala	Glu	Glu	Tyr	Lys	Ala	Asp	Phe	Thr	Glu	Cys	Cys		
20				180					185					190				
	Pro	Ala	Asp	Asp	Lys	Ala	Gly	Cys	Leu	Ile	Pro	Lys	Leu	Asp	Ala	Leu		
			195					200					205					
25	Lys	Glu	Arg	Ile	Leu	Leu	Ser	Ser	Ala	Lys	Glu	Arg	Leu	Lys	Cys	Ser		
		210					215					220						
30	Ser	Phe	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Phe	Lys	Ala	Trp	Ser	Val	Ala		
	225					230					235					240		
	Arg	Leu	Ser	Gln	Lys	Phe	Pro	Lys	Ala	Asp	Phe	Ala	Glu	Val	Ser	Lys		
35				245						250					255			
	Ile	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	Asp		
				260					265					270				
40	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Thr	Lys	Tyr	Ile	Cys		
			275					280					285					
45	Glu	His	Gln	Asp	Ser	Ile	Ser	Gly	Lys	Leu	Lys	Ala	Cys	Cys	Asp	Lys		
		290					295					300						
	Pro	Leu	Leu	Gln	Lys	Ser	His	Cys	Ile	Ala	Glu	Val	Lys	Glu	Asp	Asp		
50		305				310					315				320			
	Leu	Pro	Ser	Asp	Leu	Pro	Ala	Leu	Ala	Ala	Asp	Phe	Ala	Glu	Asp	Lys		
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55	Glu	Ile	Cys	Lys	His	Tyr	Lys	Asp	Ala	Lys	Asp	Val	Phe	Leu	Gly	Thr		
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	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Ser	Leu	
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5	Leu	Leu	Arg	Ile	Ala	Lys	Thr	Tyr	Glu	Ala	Thr	Leu	Glu	Lys	Cys	Cys	
		370					375					380					
10	Ala	Glu	Ala	Asp	Pro	Pro	Ala	Cys	Tyr	Ala	Thr	Val	Phe	Asp	Gln	Phe	
	385					390					395					400	
15	Thr	Pro	Leu	Val	Glu	Glu	Pro	Lys	Ser	Leu	Val	Lys	Lys	Asn	Cys	Asp	
					405					410					415		
20	Leu	Phe	Glu	Glu	Val	Gly	Glu	Tyr	Asp	Phe	Gln	Asn	Ala	Leu	Ile	Val	
				420					425					430			
25	Arg	Tyr	Thr	Lys	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	
			435					440					445				
30	Ile	Gly	Arg	Thr	Leu	Gly	Lys	Val	Gly	Ser	Arg	Cys	Cys	Lys	Leu	Pro	
	450						455					460					
35	Glu	Ser	Glu	Arg	Leu	Pro	Cys	Ser	Glu	Asn	His	Leu	Ala	Leu	Ala	Leu	
	465					470					475					480	
40	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Lys	Ile	
					485					490					495		
45	Thr	Lys	Cys	Cys	Thr	Asp	Ser	Leu	Ala	Glu	Arg	Arg	Pro	Cys	Phe	Ser	
				500					505					510			
50	Ala	Leu	Glu	Leu	Asp	Glu	Gly	Tyr	Ile	Pro	Lys	Glu	Phe	Lys	Ala	Glu	
		515						520					525				
55	Thr	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Pro	Glu	Asp	Glu	Lys	
	530					535						540					
60	Gln	Ile	Lys	Lys	Gln	Ser	Ala	Leu	Ala	Glu	Leu	Val	Lys	His	Lys	Pro	
	545					550					555					560	
65	Lys	Ala	Thr	Lys	Glu	Gln	Leu	Lys	Thr	Val	Leu	Gly	Asn	Phe	Ser	Ala	
					565					570					575		
70	Phe	Val	Ala	Lys	Cys	Cys	Gly	Ala	Glu	Asp	Lys	Glu	Ala	Cys	Phe	Ala	
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75	Glu	Glu	Gly	Pro	Lys	Leu	Val	Ala	Ser	Ser	Gln	Leu	Ala	Leu	Ala		
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<210> 14
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 <212> PRT
 <213> Oryctolagus cuniculus

<400> 14

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			20					25					30		
His	Arg	Phe	Asn	Asp	Val	Gly	Glu	Glu	His	Phe	Ile	Gly	Leu	Val	Leu
		35					40					45			
Ile	Thr	Phe	Ser	Gln	Tyr	Leu	Gln	Lys	Cys	Pro	Tyr	Glu	Glu	His	Ala
	50					55					60				
Lys	Leu	Val	Lys	Glu	Val	Thr	Asp	Leu	Ala	Lys	Ala	Cys	Val	Ala	Asp
65					70					75					80
Glu	Ser	Ala	Ala	Asn	Cys	Asp	Lys	Ser	Leu	His	Asp	Ile	Phe	Gly	Asp
				85					90					95	
Lys	Ile	Cys	Ala	Leu	Pro	Ser	Leu	Arg	Asp	Thr	Tyr	Gly	Asp	Val	Ala
			100					105					110		
Asp	Cys	Cys	Glu	Lys	Lys	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	His
		115					120					125			
His	Lys	Asp	Asp	Lys	Pro	Asp	Leu	Pro	Pro	Phe	Ala	Arg	Pro	Glu	Ala
	130					135					140				
Asp	Val	Leu	Cys	Lys	Ala	Phe	His	Asp	Asp	Glu	Lys	Ala	Phe	Phe	Gly
145					150					155					160
His	Tyr	Leu	Tyr	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro
				165					170					175	
Glu	Leu	Leu	Tyr	Tyr	Ala	Gln	Lys	Tyr	Lys	Ala	Ile	Leu	Thr	Glu	Cys
			180					185					190		
Cys	Glu	Ala	Ala	Asp	Lys	Gly	Ala	Cys	Leu	Thr	Pro	Lys	Leu	Asp	Ala
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Leu	Glu	Gly	Lys	Ser	Leu	Ile	Ser	Ala	Ala	Gln	Glu	Arg	Leu	Arg	Cys
	210					215					220				

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	Ala	Ser	Ile	Gln	Lys	Phe	Gly	Asp	Arg	Ala	Tyr	Lys	Ala	Trp	Ala	Leu	225	230	235	240
5	Val	Arg	Leu	Ser	Gln	Arg	Phe	Pro	Lys	Ala	Asp	Phe	Thr	Asp	Ile	Ser	245	250	255	
10	Lys	Ile	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	260	265	270	
15	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Met	275	280	285	
20	Cys	Glu	His	Gln	Glu	Thr	Ile	Ser	Ser	His	Leu	Lys	Glu	Cys	Cys	Asp	290	295	300	
25	Lys	Pro	Ile	Leu	Glu	Lys	Ala	His	Cys	Ile	Tyr	Gly	Leu	His	Asn	Asp	305	310	315	320
30	Glu	Thr	Pro	Ala	Gly	Leu	Pro	Ala	Val	Ala	Glu	Glu	Phe	Val	Glu	Asp	325	330	335	
35	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Glu	Glu	Ala	Lys	Asp	Leu	Phe	Leu	Gly	340	345	350	
40	Lys	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	355	360	365	
45	Leu	Leu	Leu	Arg	Leu	Gly	Lys	Ala	Tyr	Glu	Ala	Thr	Leu	Lys	Lys	Cys	370	375	380	
50	Cys	Ala	Thr	Asp	Asp	Pro	His	Ala	Cys	Tyr	Ala	Lys	Val	Leu	Asp	Glu	385	390	395	400
55	Phe	Gln	Pro	Leu	Val	Asp	Glu	Pro	Lys	Asn	Leu	Val	Lys	Gln	Asn	Cys	405	410	415	
	Glu	Leu	Tyr	Glu	Gln	Leu	Gly	Asp	Tyr	Asn	Phe	Gln	Asn	Ala	Leu	Leu	420	425	430	
	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	435	440	445	
	Glu	Ile	Ser	Arg	Ser	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	450	455	460	
	Pro	Glu	Ala	Glu	Arg	Leu	Pro	Cys	Val	Glu	Asp	Tyr	Leu	Ser	Val	Val	465	470	475	480

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	Leu	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Lys	485	490	495
5	Val	Thr	Lys	Cys	Cys	Ser	Glu	Ser	Leu	Val	Asp	Arg	Arg	Pro	Cys	Phe	500	505	510
10	Ser	Ala	Leu	Gly	Pro	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	515	520	525
	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Pro	Glu	Thr	Glu	530	535	540
15	Arg	Lys	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	545	550	555
20	Pro	His	Ala	Thr	Asn	Asp	Gln	Leu	Lys	Thr	Val	Val	Gly	Glu	Phe	Thr	565	570	575
25	Ala	Leu	Leu	Asp	Lys	Cys	Cys	Ser	Ala	Glu	Asp	Lys	Glu	Ala	Cys	Phe	580	585	590
	Ala	Val	Glu	Gly	Pro	Lys	Leu	Val	Glu	Ser	Ser	Lys	Ala	Thr	Leu	Gly	595	600	605
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35	<400> 15																		
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40	Glu	Asn	Phe	Gln	Gly	Leu	Val	Leu	Ile	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	20	25	30
45	Gln	Cys	Pro	Phe	Asp	Glu	His	Val	Lys	Leu	Val	Lys	Glu	Leu	Thr	Glu	35	40	45
50	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	His	Ala	Gly	Cys	Asp	Lys	50	55	60
	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Glu	Leu	Cys	Lys	Val	Ala	Thr	Leu	65	70	75
55	Arg	Glu	Thr	Tyr	Gly	Asp	Met	Ala	Asp	Cys	Cys	Glu	Lys	Gln	Glu	Pro	85	90	95

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	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Lys	His	Lys	Asp	Asp	Ser	Pro	Asp	Leu	
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5	Pro	Lys	Leu	Lys	Pro	Glu	Pro	Asp	Thr	Leu	Cys	Ala	Glu	Phe	Lys	Ala	
			115					120					125				
10	Asp	Glu	Lys	Lys	Phe	Trp	Gly	Lys	Tyr	Leu	Tyr	Glu	Val	Ala	Arg	Arg	
		130					135					140					
15	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Tyr	Tyr	Ala	Asn	Lys	Tyr	
	145					150					155					160	
20	Asn	Gly	Val	Phe	Gln	Glu	Cys	Cys	Gln	Ala	Glu	Asp	Lys	Gly	Ala	Cys	
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25	Leu	Leu	Pro	Lys	Ile	Glu	Thr	Met	Arg	Glu	Lys	Val	Leu	Ala	Ser	Ser	
				180					185					190			
30	Ala	Arg	Gln	Arg	Leu	Arg	Cys	Ala	Ser	Ile	Gln	Lys	Phe	Gly	Glu	Arg	
			195					200					205				
35	Ala	Leu	Lys	Ala	Trp	Ser	Val	Ala	Arg	Leu	Ser	Gln	Lys	Phe	Pro	Lys	
		210					215					220					
40	Ala	Asp	Phe	Thr	Asp	Val	Thr	Lys	Ile	Val	Thr	Asp	Leu	Thr	Lys	Val	
	225					230					235					240	
45	His	Lys	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	
				245						250					255		
50	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Asp	His	Gln	Asp	Thr	Leu	Ser	Ser	
				260					265					270			
55	Lys	Leu	Lys	Glu	Cys	Cys	Asp	Lys	Pro	Val	Leu	Glu	Lys	Ser	His	Cys	
			275					280					285				
60	Ile	Ala	Glu	Ile	Asp	Lys	Asp	Ala	Val	Pro	Glu	Asn	Leu	Pro	Pro	Leu	
		290					295					300					
65	Thr	Ala	Asp	Phe	Ala	Glu	Asp	Lys	Glu	Val	Cys	Lys	Asn	Tyr	Gln	Glu	
	305					310					315					320	
70	Ala	Lys	Asp	Val	Phe	Leu	Gly	Ser	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	
				325						330					335		
75	His	Pro	Glu	Tyr	Ala	Val	Ser	Val	Leu	Leu	Arg	Leu	Ala	Lys	Glu	Tyr	

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	340	345	350
5	Glu Ala Thr Leu Glu Asp Cys Cys Ala Lys Glu Asp Pro His Ala Cys 355 360 365		
10	Tyr Ala Thr Val Phe Asp Lys Leu Lys His Leu Val Asp Glu Pro Gln 370 375 380		
15	Asn Leu Ile Lys Lys Asn Cys Glu Leu Phe Glu Lys His Gly Glu Tyr 385 390 395 400		
20	Gly Phe Gln Asn Ala Leu Ile Val Arg Tyr Thr Arg Lys Ala Pro Gln 405 410 415		
25	Val Ser Thr Pro Thr Leu Val Glu Ile Ser Arg Ser Leu Gly Lys Val 420 425 430		
30	Gly Thr Lys Cys Cys Ala Lys Pro Glu Ser Glu Arg Met Pro Cys Thr 435 440 445		
35	Glu Asp Tyr Leu Ser Leu Ile Leu Asn Arg Leu Cys Val Leu His Glu 450 455 460		
40	Lys Thr Pro Val Ser Glu Lys Val Thr Lys Cys Cys Thr Glu Ser Leu 465 470 475 480		
45	Val Asn Arg Arg Pro Cys Phe Ser Asp Leu Thr Leu Asp Glu Thr Tyr 485 490 495		
50	Val Pro Lys Pro Phe Asp Gly Glu Ser Phe Thr Phe His Ala Asp Ile 500 505 510		
55	Cys Thr Leu Pro Asp Thr Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu 515 520 525		
	Val Glu Leu Leu Lys His Lys Pro Lys Ala Thr Asp Glu Gln Leu Lys 530 535 540		
	Thr Val Met Glu Asn Phe Val Ala Phe Val Asp Lys Cys Cys Ala Ala 545 550 555 560		
	Asp Asp Lys Glu Gly Cys Phe Leu Leu Glu Gly Pro Lys Leu Val Ala 565 570 575		
	Ser Thr Gln Ala Ala Leu Ala 580		

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<210> 16
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 <213> Ovis aries

<400> 16

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			20					25					30		
His	Arg	Phe	Asn	Asp	Leu	Gly	Glu	Glu	Asn	Phe	Gln	Gly	Leu	Val	Leu
		35					40					45			
Ile	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Asp	Glu	His	Val
	50					55					60				
Lys	Leu	Val	Lys	Glu	Leu	Thr	Glu	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp
65					70				75						80
Glu	Ser	His	Ala	Gly	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp
				85					90					95	
Glu	Leu	Cys	Lys	Val	Ala	Thr	Leu	Arg	Glu	Thr	Tyr	Gly	Asp	Met	Ala
			100					105					110		
Asp	Cys	Cys	Glu	Lys	Gln	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Asn
		115					120					125			
His	Lys	Asp	Asp	Ser	Pro	Asp	Leu	Pro	Lys	Leu	Lys	Pro	Glu	Pro	Asp
	130					135					140				
Thr	Leu	Cys	Ala	Glu	Phe	Lys	Ala	Asp	Glu	Lys	Lys	Phe	Trp	Gly	Lys
145					150					155					160
Tyr	Leu	Tyr	Glu	Val	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu
				165					170					175	
Leu	Leu	Tyr	Tyr	Ala	Asn	Lys	Tyr	Asn	Gly	Val	Phe	Gln	Glu	Cys	Cys
			180					185					190		
Gln	Ala	Glu	Asp	Lys	Gly	Ala	Cys	Leu	Leu	Pro	Lys	Ile	Asp	Ala	Met
		195					200					205			
Arg	Glu	Lys	Val	Leu	Ala	Ser	Ser	Ala	Arg	Gln	Arg	Leu	Arg	Cys	Ala
	210					215					220				

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	Ser	Ile	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Leu	Lys	Ala	Trp	Ser	Val	Ala	225	230	235	240
5	Arg	Leu	Ser	Gln	Lys	Phe	Pro	Lys	Ala	Asp	Phe	Thr	Asp	Val	Thr	Lys		245	250	255
10	Ile	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	Asp		260	265	270
	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys		275	280	285
15	Asp	His	Gln	Asp	Ala	Leu	Ser	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Asp	Lys		290	295	300
20	Pro	Val	Leu	Glu	Lys	Ser	His	Cys	Ile	Ala	Glu	Val	Asp	Lys	Asp	Ala	305	310	315	320
25	Val	Pro	Glu	Asn	Leu	Pro	Pro	Leu	Thr	Ala	Asp	Phe	Ala	Glu	Asp	Lys		325	330	335
	Glu	Val	Cys	Lys	Asn	Tyr	Gln	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Ser		340	345	350
30	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Glu	Tyr	Ala	Val	Ser	Val		355	360	365
35	Leu	Leu	Arg	Leu	Ala	Lys	Glu	Tyr	Glu	Ala	Thr	Leu	Glu	Asp	Cys	Cys		370	375	380
40	Ala	Lys	Glu	Asp	Pro	His	Ala	Cys	Tyr	Ala	Thr	Val	Phe	Asp	Lys	Leu	385	390	395	400
	Lys	His	Leu	Val	Asp	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Lys	Asn	Cys	Glu		405	410	415
45	Leu	Phe	Glu	Lys	His	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Leu	Ile	Val		420	425	430
50	Arg	Tyr	Thr	Arg	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu		435	440	445
	Ile	Ser	Arg	Ser	Leu	Gly	Lys	Val	Gly	Thr	Lys	Cys	Cys	Ala	Lys	Pro		450	455	460
55	Glu	Ser	Glu	Arg	Met	Pro	Cys	Thr	Glu	Asp	Tyr	Leu	Ser	Leu	Ile	Leu	465	470	475	480

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	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Lys	Val	485	490	495
5	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	500	505	510
10	Asp	Leu	Thr	Leu	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Pro	Phe	Asp	Glu	Lys	515	520	525
	Phe	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Pro	Asp	Thr	Glu	Lys	530	535	540
15	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Leu	Lys	His	Lys	Pro	545	550	555
20	Lys	Ala	Thr	Asp	Glu	Gln	Leu	Lys	Thr	Val	Met	Glu	Asn	Phe	Val	Ala	565	570	575
25	Phe	Val	Asp	Lys	Cys	Cys	Ala	Ala	Asp	Asp	Lys	Glu	Gly	Cys	Phe	Val	580	585	590
30	Leu	Glu	Gly	Pro	Lys	Leu	Val	Ala	Ser	Thr	Gln	Ala	Ala	Leu	Ala		595	600	605
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	<211>	608																	
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40	Met	Lys	Trp	Val	Thr	Phe	Ile	Ser	Leu	Phe	Phe	Leu	Phe	Ser	Ser	Ala	1	5	10
	Tyr	Ser	Arg	Gly	Leu	Val	Arg	Arg	Glu	Ala	Tyr	Lys	Ser	Glu	Ile	Ala	20	25	30
45	His	Arg	Tyr	Asn	Asp	Leu	Gly	Glu	Glu	His	Phe	Arg	Gly	Leu	Val	Leu	35	40	45
50	Val	Ala	Phe	Ser	Gln	Tyr	Leu	Gln	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	50	55	60
	Lys	Leu	Ala	Lys	Glu	Val	Thr	Glu	Phe	Ala	Lys	Ala	Cys	Ala	Ala	Glu	65	70	75
55	Glu	Ser	Gly	Ala	Asn	Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	85	90	95

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	Lys	Leu	Cys	Thr	Val	Ala	Ser	Leu	Arg	Asp	Lys	Tyr	Gly	Asp	Met	Ala	
				100					105					110			
5	Asp	Cys	Cys	Glu	Lys	Gln	Glu	Pro	Asp	Arg	Asn	Glu	Cys	Phe	Leu	Ala	
			115					120					125				
	His	Lys	Asp	Asp	Asn	Pro	Gly	Phe	Pro	Pro	Leu	Val	Ala	Pro	Glu	Pro	
10		130					135					140					
	Asp	Ala	Leu	Cys	Ala	Ala	Phe	Gln	Asp	Asn	Glu	Gln	Leu	Phe	Leu	Gly	
	145					150					155					160	
15	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	
					165					170					175		
	Glu	Leu	Leu	Tyr	Tyr	Ala	Gln	Gln	Tyr	Lys	Gly	Val	Phe	Ala	Glu	Cys	
20				180					185					190			
	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	Cys	Leu	Gly	Pro	Lys	Ile	Glu	Ala	
25			195					200					205				
	Leu	Arg	Glu	Lys	Val	Leu	Leu	Ser	Ser	Ala	Lys	Glu	Arg	Phe	Lys	Cys	
		210					215					220					
30	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Asp	Arg	Ala	Phe	Lys	Ala	Trp	Ser	Val	
	225					230					235					240	
	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	Lys	Ala	Asp	Phe	Ala	Glu	Ile	Ser	
35					245					250					255		
	Lys	Val	Val	Thr	Asp	Leu	Thr	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	
				260					265					270			
40	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Met	
			275					280					285				
45	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	Thr	Lys	Leu	Lys	Glu	Cys	Cys	Asp	
		290					295					300					
	Lys	Pro	Val	Leu	Glu	Lys	Ser	Gln	Cys	Leu	Ala	Glu	Val	Glu	Arg	Asp	
50		305				310					315					320	
	Glu	Leu	Pro	Gly	Asp	Leu	Pro	Ser	Leu	Ala	Ala	Asp	Phe	Val	Glu	Asp	
				325						330					335		
55	Lys	Glu	Val	Cys	Lys	Asn	Tyr	Gln	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	
				340					345					350			

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	Thr	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	His	Pro	Glu	Tyr	Ser	Val	Ser	
			355					360					365				
5	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Glu	Tyr	Glu	Ala	Thr	Leu	Glu	Lys	Cys	
			370				375					380					
10	Cys	Ala	Thr	Asp	Asp	Pro	Pro	Thr	Cys	Tyr	Ala	Lys	Val	Leu	Asp	Glu	
	385					390					395					400	
15	Phe	Lys	Pro	Leu	Val	Asp	Glu	Pro	Gln	Asn	Leu	Val	Lys	Thr	Asn	Cys	
					405					410					415		
20	Glu	Leu	Phe	Glu	Lys	Leu	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Leu	Leu	
				420					425					430			
25	Val	Arg	Tyr	Thr	Lys	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	
			435					440					445				
30	Glu	Val	Ser	Arg	Lys	Leu	Gly	Lys	Val	Gly	Thr	Lys	Cys	Cys	Lys	Lys	
	450						455					460					
35	Pro	Glu	Ser	Glu	Arg	Met	Ser	Cys	Ala	Glu	Asp	Phe	Leu	Ser	Val	Val	
	465					470					475					480	
40	Leu	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Arg	
					485					490					495		
45	Val	Thr	Lys	Cys	Cys	Ser	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	
				500					505					510			
50	Ser	Gly	Leu	Glu	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	
			515					520					525				
55	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	Leu	Cys	Thr	Leu	Pro	Glu	Ala	Glu	
			530				535					540					
60	Lys	Gln	Val	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Leu	Lys	His	Lys	
	545					550					555					560	
65	Pro	Lys	Ala	Thr	Asp	Glu	Gln	Leu	Lys	Thr	Val	Met	Gly	Asp	Phe	Gly	
					565					570					575		
70	Ala	Phe	Val	Glu	Lys	Cys	Cys	Ala	Ala	Glu	Asn	Lys	Glu	Gly	Cys	Phe	
				580					585					590			
75	Ser	Glu	Glu	Gly	Pro	Lys	Leu	Val	Ala	Ala	Ala	Gln	Ala	Ala	Leu	Val	

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	595	600	605
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	<212> PRT		
	<213> Gallus gallus		
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15	Thr Ser Arg Asn Leu Gln Arg Phe Ala Arg Asp Ala Glu His Lys Ser		
	20 25 30		
20	Glu Ile Ala His Arg Tyr Asn Asp Leu Lys Glu Glu Thr Phe Lys Ala		
	35 40 45		
25	Val Ala Met Ile Thr Phe Ala Gln Tyr Leu Gln Arg Cys Ser Tyr Glu		
	50 55 60		
30	Gly Leu Ser Lys Leu Val Lys Asp Val Val Asp Leu Ala Gln Lys Cys		
	65 70 75 80		
35	Val Ala Asn Glu Asp Ala Pro Glu Cys Ser Lys Pro Leu Pro Ser Ile		
	85 90 95		
40	Ile Leu Asp Glu Ile Cys Gln Val Glu Lys Leu Arg Asp Ser Tyr Gly		
	100 105 110		
45	Ala Met Ala Asp Cys Cys Ser Lys Ala Asp Pro Glu Arg Asn Glu Cys		
	115 120 125		
50	Phe Leu Ser Phe Lys Val Ser Gln Pro Asp Phe Val Gln Pro Tyr Gln		
	130 135 140		
55	Arg Pro Ala Ser Asp Val Ile Cys Gln Glu Tyr Gln Asp Asn Arg Val		
	145 150 155 160		
60	Ser Phe Leu Gly His Phe Ile Tyr Ser Val Ala Arg Arg His Pro Phe		
	165 170 175		
65	Leu Tyr Ala Pro Ala Ile Leu Ser Phe Ala Val Asp Phe Glu His Ala		
	180 185 190		
70	Leu Gln Ser Cys Cys Lys Glu Ser Asp Val Gly Ala Cys Leu Asp Thr		
	195 200 205		
75	Lys Glu Ile Val Met Arg Glu Lys Ala Lys Gly Val Ser Val Lys Gln		

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	210					215						220					
5	Gln 225	Tyr	Phe	Cys	Gly	Ile 230	Leu	Lys	Gln	Phe	Gly 235	Asp	Arg	Val	Phe	Gln 240	
10	Ala	Arg	Gln	Leu	Ile 245	Tyr	Leu	Ser	Gln	Lys 250	Tyr	Pro	Lys	Ala	Pro 255	Phe	
	Ser	Glu	Val	Ser 260	Lys	Phe	Val	His	Asp 265	Ser	Ile	Gly	Val	His 270	Lys	Glu	
15	Cys	Cys	Glu 275	Gly	Asp	Met	Val	Glu 280	Cys	Met	Asp	Asp	Met 285	Ala	Arg	Met	
20	Met 290	Ser	Asn	Leu	Cys	Ser	Gln 295	Gln	Asp	Val	Phe	Ser 300	Gly	Lys	Ile	Lys	
	Asp 305	Cys	Cys	Glu	Lys	Pro 310	Ile	Val	Glu	Arg	Ser 315	Gln	Cys	Ile	Met	Glu 320	
25	Ala	Glu	Phe	Asp	Glu 325	Lys	Pro	Ala	Asp	Leu 330	Pro	Ser	Leu	Val	Glu 335	Lys	
30	Tyr	Ile	Glu	Asp 340	Lys	Glu	Val	Cys	Lys 345	Ser	Phe	Glu	Ala	Gly 350	His	Asp	
35	Ala	Phe	Met 355	Ala	Glu	Phe	Val	Tyr 360	Glu	Tyr	Ser	Arg	Arg 365	His	Pro	Glu	
	Phe 370	Ser	Ile	Gln	Leu	Ile	Met 375	Arg	Ile	Ala	Lys	Gly 380	Tyr	Glu	Ser	Leu	
40	Leu 385	Glu	Lys	Cys	Cys	Lys 390	Thr	Asp	Asn	Pro	Ala 395	Glu	Cys	Tyr	Ala	Asn 400	
45	Ala	Gln	Glu	Gln 405	Leu	Asn	Gln	His	Ile 410	Lys	Glu	Thr	Gln	Asp 415	Val	Val	
	Lys	Thr	Asn	Cys 420	Asp	Leu	Leu	His	Asp 425	His	Gly	Glu	Ala	Asp 430	Phe	Leu	
50	Lys	Ser	Ile 435	Leu	Ile	Arg	Tyr	Thr 440	Lys	Lys	Met	Pro	Gln 445	Val	Pro	Thr	
55	Asp 450	Leu	Leu	Leu	Glu	Thr	Gly 455	Lys	Lys	Met	Thr 460	Thr	Ile	Gly	Thr	Lys	

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	Cys	Cys	Gln	Leu	Gly	Glu	Asp	Arg	Arg	Met	Ala	Cys	Ser	Glu	Gly	Tyr	465	470	475	480
5	Leu	Ser	Ile	Val	Ile	His	Asp	Thr	Cys	Arg	Lys	Gln	Glu	Thr	Thr	Pro		485	490	495
10	Ile	Asn	Asp	Asn	Val	Ser	Gln	Cys	Cys	Ser	Gln	Leu	Tyr	Ala	Asn	Arg		500	505	510
15	Arg	Pro	Cys	Phe	Thr	Ala	Met	Gly	Val	Asp	Thr	Lys	Tyr	Val	Pro	Pro		515	520	525
20	Pro	Phe	Asn	Pro	Asp	Met	Phe	Ser	Phe	Asp	Glu	Lys	Leu	Cys	Ser	Ala		530	535	540
25	Pro	Ala	Glu	Glu	Arg	Glu	Val	Gly	Gln	Met	Lys	Leu	Leu	Ile	Asn	Leu		545	550	555
30	Ile	Lys	Arg	Lys	Pro	Gln	Met	Thr	Glu	Glu	Gln	Ile	Lys	Thr	Ile	Ala		565	570	575
35	Asp	Gly	Phe	Thr	Ala	Met	Val	Asp	Lys	Cys	Cys	Lys	Gln	Ser	Asp	Ile		580	585	590
40	Asn	Thr	Cys	Phe	Gly	Glu	Glu	Gly	Ala	Asn	Leu	Ile	Val	Gln	Ser	Arg		595	600	605
45	Ala	Thr	Leu	Gly	Ile	Gly	Ala										610	615		
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60	Tyr	Ser	Arg	Gly	Val	Phe	Arg	Arg	Asp	Thr	Tyr	Lys	Ser	Glu	Ile	Ala		20	25	30
65	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	Gln	Tyr	Phe	Lys	Gly	Leu	Val	Leu		35	40	45
70	Ile	Ala	Phe	Ser	Gln	His	Leu	Gln	Gln	Cys	Pro	Tyr	Glu	Glu	His	Val	50	55	60	

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	Lys	Leu	Val	Arg	Glu	Val	Thr	Glu	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	65	70	75	80
5	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	Ser	Ile	His	Thr	Leu	Phe	Gly	Asp	85	90		95
10	Lys	Leu	Cys	Ala	Ile	Pro	Ser	Leu	Arg	Glu	His	Tyr	Gly	Asp	Leu	Ala	100	105		110
15	Asp	Cys	Cys	Glu	Lys	Glu	Glu	Pro	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	115	120		125
20	His	Lys	Asn	Asp	Asn	Pro	Asp	Ile	Pro	Lys	Leu	Lys	Pro	Asp	Pro	Val	130	135		140
25	Ala	Leu	Cys	Ala	Asp	Phe	Gln	Glu	Asp	Glu	Gln	Lys	Phe	Trp	Gly	Lys	145	150		155
30	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	165	170		175
35	Leu	Leu	Tyr	Tyr	Ala	Ile	Ile	Tyr	Lys	Asp	Val	Phe	Ser	Glu	Cys	Cys	180	185		190
40	Gln	Ala	Ala	Asp	Lys	Ala	Ala	Cys	Leu	Leu	Pro	Lys	Ile	Glu	His	Leu	195	200		205
45	Arg	Glu	Lys	Val	Leu	Thr	Ser	Ala	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	210	215		220
50	Ser	Ile	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Phe	Lys	Ala	Trp	Ser	Leu	Ala	225	230		235
55	Arg	Leu	Ser	Gln	Arg	Phe	Pro	Lys	Ala	Asp	Phe	Thr	Glu	Ile	Ser	Lys	245	250		255
	Ile	Val	Thr	Asp	Leu	Ala	Lys	Val	His	Lys	Glu	Cys	Cys	His	Gly	Asp	260	265		270
	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	275	280		285
	Glu	Asn	Gln	Asp	Thr	Ile	Ser	Thr	Lys	Leu	Lys	Glu	Cys	Cys	Asp	Lys	290	295		300
	Pro	Leu	Leu	Glu	Lys	Ser	His	Cys	Ile	Ala	Glu	Ala	Lys	Arg	Asp	Glu	305	310		315

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	Leu	Pro	Ala	Asp	Leu	Asn	Pro	Leu	Glu	His	Asp	Phe	Val	Glu	Asp	Lys	
					325					330					335		
5	Glu	Val	Cys	Lys	Asn	Tyr	Lys	Glu	Ala	Lys	His	Val	Phe	Leu	Gly	Thr	
				340					345					350			
	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Ser	Leu	
10			355					360					365				
	Leu	Leu	Arg	Ile	Ala	Lys	Ile	Tyr	Glu	Ala	Thr	Leu	Glu	Asp	Cys	Cys	
		370					375					380					
15	Ala	Lys	Glu	Asp	Pro	Pro	Ala	Cys	Tyr	Ala	Thr	Val	Phe	Asp	Lys	Phe	
	385					390					395					400	
	Gln	Pro	Leu	Val	Asp	Glu	Pro	Lys	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	
20					405					410					415		
	Leu	Phe	Glu	Lys	Leu	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Leu	Ile	Val	
25				420					425					430			
	Arg	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	
			435					440					445				
30	Val	Ala	Arg	Lys	Leu	Gly	Leu	Val	Gly	Ser	Arg	Cys	Cys	Lys	Arg	Pro	
		450					455					460					
	Glu	Glu	Glu	Arg	Leu	Ser	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Leu	Val	Leu	
35	465					470					475					480	
	Asn	Arg	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	Lys	Val	
				485						490					495		
40	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	
				500					505					510			
45	Ala	Leu	Thr	Pro	Asp	Glu	Thr	Tyr	Lys	Pro	Lys	Glu	Phe	Val	Glu	Gly	
			515					520					525				
	Thr	Phe	Thr	Phe	His	Ala	Asp	Leu	Cys	Thr	Leu	Pro	Glu	Asp	Glu	Lys	
50		530					535					540					
	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Leu	Lys	His	Lys	Pro	
	545					550					555					560	
55	His	Ala	Thr	Glu	Glu	Gln	Leu	Arg	Thr	Val	Leu	Gly	Asn	Phe	Ala	Ala	
				565						570					575		

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Phe Val Gln Lys Cys Cys Ala Ala Pro Asp His Glu Ala Cys Phe Ala
580 585 590

5 Val Glu Gly Pro Lys Phe Val Ile Glu Ile Arg Gly Ile Leu Ala
595 600 605

10 <210> 20
<211> 584
<212> PRT
<213> artificial sequence

15 <220>
<223> N terminal is residues 1 to 572 of HSA. C terminal is residues
573 to 584 of Macaque albumin.

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1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

25 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

30 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

35 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

40 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

45 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

50 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

55 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

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	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
5	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
10		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
20				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
25			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
30	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
35					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
40				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
45	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
	370						375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
50	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
55	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	

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	420	425	430
5	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys 435 440 445		
10	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His 450 455 460		
	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser 465 470 475 480		
15	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr 485 490 495		
20	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp 500 505 510		
	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala 515 520 525		
25	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu 530 535 540		
30	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys 545 550 555 560		
	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Phe Val 565 570 575		
35	Ala Ala Ser Gln Ala Ala Leu Ala 580		
40	<210> 21 <211> 584 <212> PRT <213> Artificial Sequence		
45	<220> <223> N terminal is residues 1 to 572 from HSA. C terminal is residues 573 to 584 from mouse albumin.		
	<400> 21		
50	Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu 1 5 10 15		
	Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln 20 25 30		
55	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu		

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	35	40	45
5	Phe 50	Ala 55	Asn 60
	Ala Lys Thr Cys Val	Asp Glu Ser	Ala Glu Asn Cys Asp Lys
10	Ser 65	Phe 70	Cys 75
	Leu His Thr Leu	Gly Asp Lys Leu	Thr Val Ala Thr Leu
15	Arg 85	Glu Met	Cys 90
	Glu Thr Tyr Gly	Ala Asp Cys Cys	Ala Lys Gln Glu Pro
20	Glu 100	Phe Leu	Asp 110
	Arg Asn Glu Cys	Gln His Lys Asp	Asn Pro Asn Leu
25	Pro 115	Val Arg	Cys 125
	Arg Leu Val Arg	Pro Glu Val Asp	Val Met Cys Thr Ala Phe His
30	Asp 130	Phe Leu	Tyr 140
	Asn Glu Glu Thr	Lys Lys Tyr Leu	Tyr Glu Ile Ala Arg
35	Arg 145	Tyr Ala	Leu 155
	His Pro Tyr Phe	Pro Glu Leu Leu	Phe Phe Ala Lys Arg
40	Tyr 165	Thr Glu	Cys 170
	Lys Ala Ala Phe	Cys Cys Gln Ala	Ala Asp Lys Ala Ala
45	Cys 180	Leu Asp	Glu 185
	Leu Leu Pro Lys	Leu Arg Asp Glu	Gly Lys Ala Ser
50	Ser 195	Leu Lys	Cys 200
	Ala Lys Gln Arg	Leu Cys Ala Ser	Leu Gln Lys Phe Gly Glu
55	Arg 210	Ala Trp	Val 215
	Ala Phe Lys Ala	Val Ala Arg Leu	Ser Gln Arg Phe Pro
60	Lys 225	Glu Val	Ser 235
	Ala Glu Phe Ala	Ser Lys Leu Val	Thr Asp Leu Thr Lys
65	Val 245	Cys Cys	His 250
	His Thr Glu Cys	Gly Asp Leu Leu	Glu Cys Ala Asp Asp
70	Arg 260	Lys Tyr	Ile 265
	Ala Asp Leu Ala	Cys Glu Asn Gln	Asp Ser Ile Ser
75	Ser 275	Glu Cys	Glu 285
	Lys Leu Lys Glu	Cys Cys Glu Lys	Pro Leu Leu Glu Lys Ser His

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	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
5	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
10					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
15	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
20		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
25	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
35			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
40	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
45				485						490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
50				500					505					510			
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
55	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
	530						535					540					

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Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

5 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Asn Leu Val
565 570 575

10 Thr Arg Cys Lys Asp Ala Leu Ala
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<210> 22

<211> 584

<212> PRT

15 <213> Artificial Sequence

<220>

<223> N terminal is residues 1 to 572 of HSA. C terminal is residues
573 to 584 of rabbit albumin.

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Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

25 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

30 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

35 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

40 Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

45 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

50 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

55 Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

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	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
5	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
10			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
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15	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
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	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
20					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
25	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
30		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
35	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
40	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
45			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
50	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
55				405						410					415		

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	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
5	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
10		450					455					460					
	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
15																	
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
					485					490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
20				500					505					510			
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
25			515					520					525				
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
		530					535					540					
30																	
	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
35					565					570					575		
	Glu	Ser	Ser	Lys	Ala	Thr	Leu	Gly									
40				580													
	<210>	23															
	<211>	584															
	<212>	PRT															
45	<213>	Artificial Sequence															
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	<223>	N-terminal is residues 1 to 572 of HSA. C-terminal is residues 573 to 583 of sheep albumin.															
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	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	
				20					25					30			

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	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
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5	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
10	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
15	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
20	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
30	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
35	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
40	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
45	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
50	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
55	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
60	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
65	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
70	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
75	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	

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10	Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala 305 310 315 320		
15	Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg 325 330 335		
20	Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr 340 345 350		
25	Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu 355 360 365		
30	Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro 370 375 380		
35	Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu 385 390 395 400		
40	Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro 405 410 415		
45	Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys 420 425 430		
50	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys 435 440 445		
55	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His 450 455 460		
	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser 465 470 475 480		
	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr 485 490 495		
	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp 500 505 510		
	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala 515 520 525		

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Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
 530 535 540

5 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
 545 550 555 560

10 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
 565 570 575

Ala Ser Thr Gln Ala Ala Leu Ala
 580

15 <210> 24
 <211> 399
 <212> PRT
 <213> Artificial sequence

20 <220>
 <223> Artificial albumin variant: human serum albumin domain 1 and
 human serum albumin domain 3

25 <400> 24

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
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30 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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35 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60

40 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

45 Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

50 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
 100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
 115 120 125

55 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
 130 135 140

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	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
5	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
10	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
15	Ser	Ala	Val	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	
			195					200					205				
20	Phe	Glu	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	
	210						215					220					
25	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	
	225					230					235					240	
30	Ser	Arg	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	
					245					250					255		
35	Ala	Lys	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	
				260					265					270			
40	Gln	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	
			275					280					285				
45	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	
	290						295					300					
50	Leu	Glu	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	
	305					310					315					320	
55	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	
					325					330					335		
60	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	
				340					345					350			
65	Ala	Thr	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	
			355					360					365				
70	Val	Glu	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	
	370						375					380					
75	Glu	Gly	Lys	Lys	Leu	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu		
	385					390					395						

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<210> 25
 <211> 403
 <212> PRT
 <213> Artificial sequence

<220>
 <223> Artificial albumin variant: human serum albumin domain 2 and human serum albumin domain 3

<400> 25

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
 1 5 10 15

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
 20 25 30

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
 35 40 45

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
 50 55 60

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
 65 70 75 80

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
 85 90 95

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
 100 105 110

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
 115 120 125

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
 130 135 140

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
 145 150 155 160

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
 165 170 175

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
 180 185 190

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
 195 200 205

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	Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala	
	210	215 220
5	Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr	
	225	230 235 240
10	Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys	
		245 250 255
15	Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser	
		260 265 270
20	Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser	
		275 280 285
25	Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro	
		290 295 300
30	Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe	
	305	310 315 320
35	Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu	
		325 330 335
40	Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys	
		340 345 350
45	His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp	
		355 360 365
50	Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr	
	370	375 380
55	Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala	
	385	390 395 400
	Leu Gly Leu	
	<210> 26	
	<211> 410	
	<212> PRT	
	<213> Artificial sequence	
	<220>	
	<223> Artificial albumin variant: two consecutive copies of human serum	
	albumin domain 3	
	<400> 26	

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	Val	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	
	1				5					10					15		
5	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	
				20					25					30			
10	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	
			35					40					45				
15	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	
		50					55					60					
20	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	
	65					70					75					80	
25	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	
				85						90					95		
30	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	
				100					105					110			
35	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	
			115					120					125				
40	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	
		130					135					140					
45	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	
	145					150					155					160	
50	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	
				165					170						175		
55	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	
				180					185					190			
60	Lys	Lys	Leu	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu	Val	Glu	Glu	
			195					200					205				
65	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	
		210					215					220					
70	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	
	225					230					235					240	
75	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	
				245						250					255		

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	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	
				260					265					270			
5	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	
			275					280					285				
10	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	
		290					295					300					
15	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	
	305					310					315					320	
20	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	
					325					330					335		
25	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	
				340					345					350			
30	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	
			355					360					365				
35	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	
	370						375					380					
40	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	
	385					390					395					400	
45	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu							
					405					410							
50	<210>	27															
	<211>	205															
	<212>	PRT															
	<213>	Artificial sequence															
55	<220>																
	<223>	Artificial albumin variant: human serum albumin domain 3															
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	1				5					10					15		
65	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	
				20					25					30			
70	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	
			35					40					45				

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	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	
	50						55					60					
5	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	
	65					70					75					80	
10	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	
					85					90					95		
15	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	
				100					105					110			
20	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	
		115						120					125				
25	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	
	130						135					140					
30	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	
	145					150					155					160	
35	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	
					165					170					175		
40	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	
				180					185					190			
45	Lys	Lys	Leu	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu				
			195					200					205				
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	<212>	PRT															
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55	<220>																
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	<400>	28															
60	Val	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	
	1				5					10					15		
65	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	
				20					25					30			
70	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	
			35					40					45				

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	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	
	50						55					60					
5	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	
	65					70					75					80	
	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	
10					85					90					95		
	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	
				100					105					110			
15	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	
			115					120					125				
	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	
20		130					135					140					
	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	
25	145					150					155					160	
	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	
					165					170					175		
30	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	
				180					185					190			
	Lys	Lys	Leu	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu	Val	Glu	Glu	
35			195					200					205				
	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	
		210					215					220					
40	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	
	225					230					235					240	
	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	
45					245					250					255		
	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	
50				260					265					270			
	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	
			275					280					285				
55	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	
	290						295					300					

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	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	305	310	315	320
5	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	325	330	335	
10	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	340	345	350	
15	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	355	360	365	
20	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	370	375	380	
25	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	385	390	395	400
30	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu	Val	Glu	Glu	Pro	Gln	Asn	405	410	415	
35	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	Tyr	Lys	420	425	430	
40	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	435	440	445	
45	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	Val	Gly	450	455	460	
50	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	Ala	Glu	465	470	475	480
55	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	Glu	Lys	485	490	495	
	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	500	505	510	
	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	Tyr	Val	515	520	525	
	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	530	535	540	
	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	545	550	555	560

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	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	Lys	Ala	565	570	575	
5	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	Ala	Asp	580	585	590	
10	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val	Ala	Ala	595	600	605	
15	Ser	Gln	Ala	Ala	Leu	Gly	Leu	610	615											
20	<210>	29																		
	<211>	604																		
	<212>	PRT																		
	<213>	Artificial Sequence																		
25	<220>																			
	<223>	HSA Domain I + HSA Domain III + HSA Domain III																		
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	Asp	Ala	His	Lys	Ser	Glu	Val	Ala	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu	1	5	10	15
35	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	20	25	30	
40	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	35	40	45	
45	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	50	55	60	
50	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	65	70	75	80
55	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	85	90	95	
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	100	105	110	
	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	115	120	125	
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	130	135	140	

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	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	145	150	155	160
5	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	165	170	175	
10	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	180	185	190	
	Ser	Ala	Val	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	195	200	205	
15	Phe	Glu	Gln	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	210	215	220	
20	Tyr	Thr	Lys	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	225	230	235	240
	Ser	Arg	Asn	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	245	250	255	
25	Ala	Lys	Arg	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	260	265	270	
30	Gln	Leu	Cys	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	275	280	285	
35	Lys	Cys	Cys	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	290	295	300	
	Leu	Glu	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	305	310	315	320
40	Phe	Thr	Phe	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	325	330	335	
45	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	340	345	350	
	Ala	Thr	Lys	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	355	360	365	
50	Val	Glu	Lys	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	370	375	380	
55	Glu	Gly	Lys	Lys	Leu	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu	Val	385	390	395	400

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	Glu	Glu	Pro	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	
					405					410					415		
5	Leu	Gly	Glu	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	
				420					425					430			
10	Lys	Val	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	
			435					440					445				
15	Leu	Gly	Lys	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	
		450					455					460					
20	Met	Pro	Cys	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	
	465					470					475					480	
25	Val	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	
					485					490					495		
30	Thr	Glu	Ser	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	
				500					505					510			
35	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	
			515					520					525				
40	His	Ala	Asp	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	
		530					535					540					
45	Gln	Thr	Ala	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	
	545					550					555					560	
50	Glu	Gln	Leu	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	
					565					570					575		
55	Cys	Cys	Lys	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	
				580				585					590				
60	Lys	Leu	Val	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu					
			595					600									
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<223> Truncated heavy chain of the major histocompatibility complex class I-like Fc receptor (FCGRT) (together, SEQ ID No. 30 and SEQ ID No. 31 form FcRN)

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10 Leu Leu Pro Gly Ser Leu Gly Ala Glu Ser His Leu Ser Leu Leu Tyr
20 25 30

His Leu Thr Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp
15 35 40 45

Val Ser Gly Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu
50 55 60

20 Arg Gly Glu Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val
65 70 75 80

25 Ser Trp Tyr Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys
85 90 95

Leu Phe Leu Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr
100 105 110

30 Leu Gln Gly Leu Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val
115 120 125

35 Pro Thr Ala Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp
130 135 140

40 Leu Lys Gln Gly Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile
145 150 155 160

Ser Gln Arg Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr
165 170 175

45 Phe Leu Leu Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg
180 185 190

50 Gly Arg Gly Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys
195 200 205

Ala Arg Pro Ser Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe
210 215 220

55 Ser Phe Tyr Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu

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	225		230		235		240									
5	Ala	Ala	Gly	Thr	Gly	Gln	Gly	Asp	Phe	Gly	Pro	Asn	Ser	Asp	Gly	Ser
					245					250					255	
10	Phe	His	Ala	Ser	Ser	Ser	Leu	Thr	Val	Lys	Ser	Gly	Asp	Glu	His	His
				260					265					270		
15	Tyr	Cys	Cys	Ile	Val	Gln	His	Ala	Gly	Leu	Ala	Gln	Pro	Leu	Arg	Val
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40	Gly	Leu	Glu	Ala	Ile	Gln	Arg	Thr	Pro	Lys	Ile	Gln	Val	Tyr	Ser	Arg
				20					25					30		
45	His	Pro	Ala	Glu	Asn	Gly	Lys	Ser	Asn	Phe	Leu	Asn	Cys	Tyr	Val	Ser
			35					40					45			
50	Gly	Phe	His	Pro	Ser	Asp	Ile	Glu	Val	Asp	Leu	Leu	Lys	Asn	Gly	Glu
	50						55					60				
55	Arg	Ile	Glu	Lys	Val	Glu	His	Ser	Asp	Leu	Ser	Phe	Ser	Lys	Asp	Trp
	65					70					75				80	
60	Ser	Phe	Tyr	Leu	Leu	Tyr	Tyr	Thr	Glu	Phe	Thr	Pro	Thr	Glu	Lys	Asp
				85					90						95	
65	Glu	Tyr	Ala	Cys	Arg	Val	Asn	His	Val	Thr	Leu	Ser	Gln	Pro	Lys	Ile
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

Arg Glu Asn Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Glu Leu
 100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
 115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
 130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
 145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
 165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
 180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
 195 200 205

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	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
	210						215					220					
5	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
10					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
15	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
20		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
25																	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
30	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
35			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
40																	
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
45	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
50				420					425					430			
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
55																	
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
	450						455					460					

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	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	465	470	475	480
5	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr		485	490	495
10	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp		500	505	510
15	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala		515	520	525
20	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu		530	535	540
25	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys		545	550	555
30	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val		565	570	575
35	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu									580	585	
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	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln		20	25	30
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu		35	40	45
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys		50	55	60
	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	65	70	75	80

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	Arg	Glu	Asn	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
5	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Glu	Leu	
				100					105					110			
	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
10			115					120					125				
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
15	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
20					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
25				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
30	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
35		225				230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
40	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
45	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
50		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
55	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
				325						330					335		

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	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
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5	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
10	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
15	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
20	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
25	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
30	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
35	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
40	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
45	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
					485					490					495		
50	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
55	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
60	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
		530					535					540					
65	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
70	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
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75	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu								

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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20

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

25

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

30

Arg Glu Asn Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

35

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
 100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
 115 120 125

40

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
 130 135 140

45

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
 145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
 165 170 175

50

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
 180 185 190

55

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
 195 200 205

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	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
	210						215					220					
5	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
10	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
15	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
20	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
25	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
30	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
35	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
40	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
45	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
50	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
	370						375					380					
55	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
60	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
65	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
70	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
75	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	

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	450		455		460
5	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser				
	465		470		475 480
10	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr				
		485		490	495
15	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp				
		500		505	510
20	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala				
		515		520	525
25	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu				
		530		535	540
30	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys				
		545		550	555 560
35	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val				
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65	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu				
		35		40	45
70	Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys				
		50		55	60
75	Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu				
		65		70	75 80

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	Arg	Glu	Lys	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
5	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
10			115					120					125				
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
15																	
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
20	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
25				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
30																	
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
35	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
40																	
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
45	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
50		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
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55																	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	

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	325				330				335							
5	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr
				340					345					350		
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu
10			355					360					365			
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro
		370					375					380				
15	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu
	385					390					395					400
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro
20					405					410					415	
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys
				420					425					430		
25	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys
			435					440					445			
30	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His
		450					455					460				
	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser
35	465					470					475					480
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr
					485					490					495	
40	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp
				500					505					510		
45	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala
			515					520					525			
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu
50		530					535					540				
	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys
	545					550					555					560
55	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val
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Ala Ala Ser Gln Ala Ala Leu Gly Leu
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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20 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

25 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

30 Arg Ala Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

35 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

40 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

45 Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

50 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

55 Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu

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	195	200	205
5	Arg Ala Phe Lys Ala Trp 210	Ala Val Ala Arg Leu 215	Ser Gln Arg Phe Pro 220
10	Lys Ala Glu Phe Ala Glu 225	Val Ser Lys Leu Val 230	Thr Asp Leu Thr Lys 235 240
15	Val His Thr Glu Cys Cys 245	His Gly Asp Leu Leu 250	Glu Cys Ala Asp Asp 255
20	Arg Ala Asp Leu Ala Lys Tyr 260	Ile Cys Glu Asn Gln 265	Asp Ser Ile Ser 270
25	Ser Lys Leu Lys Glu Cys Cys 275	Glu Lys Pro Leu Leu 280	Glu Lys Ser His 285
30	Cys Ile Ala Glu Val Glu 290	Asn Asp Glu Met Pro 295	Ala Asp Leu Pro Ser 300
35	Leu Ala Ala Asp Phe Val 305	Glu Ser Lys Asp Val 310	Cys Lys Asn Tyr Ala 315 320
40	Glu Ala Lys Asp Val Phe 325	Leu Gly Met Phe Leu 330	Tyr Glu Tyr Ala Arg 335
45	Arg His Pro Asp Tyr Ser 340	Val Val Leu Leu Arg 345	Leu Ala Lys Thr 350
50	Tyr Glu Thr Thr Leu Glu 355	Lys Cys Cys Ala Ala 360	Ala Asp Pro His Glu 365
55	Cys Tyr Ala Lys Val Phe 370	Asp Glu Phe Lys Pro 375	Leu Val Glu Glu Pro 380
	Gln Asn Leu Ile Lys 385	Gln Asn Cys Glu Leu 390	Phe Glu Gln Leu Gly Glu 395 400
	Tyr Lys Phe Gln Asn Ala 405	Leu Leu Val Arg Tyr 410	Thr Lys Lys Val Pro 415
	Gln Val Ser Thr Pro Thr 420	Leu Val Glu Val Ser 425	Arg Asn Leu Gly Lys 430
	Val Gly Ser Lys Cys Cys 435	Lys His Pro Glu Ala 440	Lys Arg Met Pro Cys 445

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	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
	450						455					460					
5	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
10					485					490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
15	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
20			530				535					540					
	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
25	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val	
					565					570					575		
30	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu								
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45	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	
				20					25					30			
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
50			35					40					45				
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
	50						55					60					
55	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	

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	65					70						75				80
5	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
10	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Phe
				100					105					110		
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
20	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
		130					135					140				
25	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145					150					155					160
30	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	
35	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser
				180					185					190		
40	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
45	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
	210					215						220				
50	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys
	225					230					235					240
55	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
					245					250					255	
60	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser
				260					265					270		
65	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His
			275					280					285			
70	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser
		290					295					300				
75	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala
	305					310					315					320

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	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
5	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
10	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
15	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
20	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
25	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
35	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
40	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
45	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
50	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485						490					495		
55	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
60	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
65	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
		530					535					540					
70	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
75	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val	
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EP 3 330 283 A2

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

5 <210> 38
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10 <220>
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<400> 38

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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20 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

25 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

30 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Lys Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

35 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

40 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

45 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

50 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

55 Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

EP 3 330 283 A2

	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
5	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
10	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
20	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
25	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
30	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
35	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
40	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
45	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
50	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
55	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
	370						375					380					
60	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
65	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
70	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
75	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				

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Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

5 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

10 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

15 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

20 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

25 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

30 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

50 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

55 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

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5	Arg	Ala	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	85	90	95	
10	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	100	105	110	
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	115	120	125	
20	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	130	135	140	
25	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	145	150	155	160
30	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	165	170	175	
35	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	180	185	190	
40	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	195	200	205	
45	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	210	215	220	
50	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	225	230	235	240
55	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	245	250	255	
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	260	265	270	
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	275	280	285	
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	290	295	300	
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	305	310	315	320

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5	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
10	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
15	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
20	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
25	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
35	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
40	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
45	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
50	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485						490					495		
55	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
60	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
65	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
		530					535					540					
70	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
75	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
				565						570					575		

EP 3 330 283 A2

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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<211> 585
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10 <220>
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

25 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

30 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Phe
100 105 110

40 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

45 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

50 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

55 Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

EP 3 330 283 A2

	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
5	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
10	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
15	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
20	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
25	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
30	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
35	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
40	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
	370						375					380					
45	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
50	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
					420				425					430			
55	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				

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Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

5 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

10 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

15 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

20 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

25 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

30 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
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Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

50 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

55 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

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	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
5	Arg	Asp	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
10	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
20	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
	130						135					140					
25	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
30	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
35	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
40	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
45	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
	210						215					220					
50	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
55	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
				245						250					255		
60	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
65	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
70	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
75	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	

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	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
5	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
10	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
15	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
20	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
25	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
35	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
40	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
45	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
50	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485						490					495		
55	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
60	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
65	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
		530					535					540					
70	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
75	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val	

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565

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Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

25

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

30

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

35

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

40

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Gly Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

45

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

50

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

55

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

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	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
5	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
		210					215					220				
10	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys
	225					230					235					240
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
					245					250					255	
20	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser
			260						265					270		
25	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His
			275					280					285			
30	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser
	290						295					300				
35	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala
	305					310					315					320
40	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg
				325						330					335	
45	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr
			340						345					350		
50	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu
		355						360					365			
55	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro
	370						375					380				
60	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu
	385					390					395					400
65	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro
				405						410					415	
70	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys
				420					425					430		
75	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys

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	435	440	445
5	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His 450 455 460		
10	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser 465 470 475 480		
15	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr 485 490 495		
20	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp 500 505 510		
25	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala 515 520 525		
30	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu 530 535 540		
35	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys 545 550 555 560		
40	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val 565 570 575		
45	Ala Ala Ser Gln Ala Ala Leu Gly Leu 580 585		
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70	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu 35 40 45		
75	Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys 50 55 60		

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	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	65	70	75	80
5	Arg	Asp	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	85	90	95	
10	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	100	105	110	
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	115	120	125	
20	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	130	135	140	
25	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	145	150	155	160
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	165	170	175	
30	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	180	185	190	
35	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	195	200	205	
40	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	210	215	220	
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	225	230	235	240
45	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	245	250	255	
50	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	260	265	270	
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	275	280	285	
55	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	290	295	300	
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala				

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	305		310		315		320									
5	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg
					325					330					335	
10	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr
				340					345					350		
15	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu
			355					360					365			
20	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro
		370					375					380				
25	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu
	385					390					395					400
30	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro
				405						410					415	
35	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys
				420					425					430		
40	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys
			435					440					445			
45	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His
	450						455					460				
50	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser
	465					470					475				480	
55	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr
				485						490					495	
60	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp
				500					505					510		
65	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala
			515					520					525			
70	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu
	530						535					540				
75	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys
	545					550					555					560

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	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val
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5	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu							
				580					585							
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	1				5					10					15	
20	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln
				20					25					30		
25	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
			35					40					45			
30	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
		50					55					60				
35	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
	65					70					75					80
40	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
45	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Gly	Asn	Leu
				100					105					110		
50	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
55	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
		130					135					140				
60	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145					150					155					160
65	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	
70	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser

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	180		185		190												
5	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
10	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
15	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
20	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
25	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
30	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
35	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
40	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
45	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
				325						330					335		
50	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
55	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
60	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
65	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
70	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
75	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			

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	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
5	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
10		465				470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
					485					490					495		
15	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
20			515					520					525				
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
		530					535					540					
25	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
		545				550					555					560	
	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
30					565					570					575		
	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu								
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	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	
50				20					25					30			
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
			35					40					45				
55	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	

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	50		55		60												
5	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
10					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
20		130					135					140					
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
25	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
30	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
35			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
40	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
45					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
50	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
55	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					

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	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	305	310	315	320
5	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg		325	330	335
10	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr		340	345	350
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu		355	360	365
15	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro		370	375	380
20	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu		385	390	395
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro		405	410	415
25	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys		420	425	430
30	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys		435	440	445
35	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His		450	455	460
	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser		465	470	475
40	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr		485	490	495
45	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Gln	Thr	Phe	Thr	Phe	His	Ala	Asp		500	505	510
50	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala		515	520	525
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu		530	535	540
55	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys		545	550	555
																				560

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Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

5 Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

25 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

30 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

35 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

40 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asp Leu
100 105 110

45 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

50 Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

55 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

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	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
5	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
10		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
20				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
25			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
30	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
35					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
40	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
45		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
50	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
55	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			

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Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

5 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

10 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

15 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

20 Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

25 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

30 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

35 Ala Ala Ser Gln Ala Ala Leu Gly Leu
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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55 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

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	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
	50						55					60					
5	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
10					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
20		130					135					140					
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
25																	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
30	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
35			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
40																	
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
45					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
50																	
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
55	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					

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	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	305	310	315	320
5	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg		325	330	335
10	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr		340	345	350
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu		355	360	365
15	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro		370	375	380
20	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	385	390	395	400
25	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro		405	410	415
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys		420	425	430
30	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys		435	440	445
35	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His		450	455	460
40	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	465	470	475	480
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr		485	490	495
45	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp		500	505	510
50	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Met	Ala		515	520	525
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu		530	535	540
55	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	545	550	555	560

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Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

5 Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

25 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

30 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

35 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

40 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Gly Leu
100 105 110

45 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

50 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

55 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

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	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
5	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
10		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
20				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
25			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
30	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
35					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
40	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
45		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
50	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
55	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			

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Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

5 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

10 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

15 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

20 Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

25 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

30 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

35 Ala Ala Ser Gln Ala Ala Leu Gly Leu
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55 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

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	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
	50						55					60					
5	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
10					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	His	Leu	
				100					105					110			
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120						125			
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
20		130					135					140					
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145				150						155					160	
25	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
30	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
35			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210				215						220					
40	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225				230						235				240		
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
45				245						250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
50	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
55	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290				295						300					

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	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	305	310	315	320
5	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg		325	330	335
10	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr		340	345	350
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu		355	360	365
15	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro		370	375	380
20	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu		385	390	395
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro		405	410	415
25	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys		420	425	430
30	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys		435	440	445
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His		450	455	460
35	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser		465	470	475
40	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr		485	490	495
45	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp		500	505	510
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala		515	520	525
50	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu		530	535	540
55	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys				

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	545		550		555		560									
5	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val
				565						570					575	
10	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu							
				580					585							
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	<223>	HSA H512E														
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	1				5					10					15	
25	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln
				20					25					30		
30	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
			35					40					45			
35	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
	50						55					60				
40	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
	65					70					75					80
45	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
50	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu
				100					105					110		
55	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
	130						135					140				
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145					150					155					160
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	

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	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
5	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
10		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
15	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
20				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
25			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
30	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
35					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
40				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
45	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
	370						375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
50	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
55	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	

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	420	425	430
5	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys 435 440 445		
10	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His 450 455 460		
15	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser 465 470 475 480		
20	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr 485 490 495		
25	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Glu 500 505 510		
30	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala 515 520 525		
35	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu 530 535 540		
40	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys 545 550 555 560		
45	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val 565 570 575		
50	Ala Ala Ser Gln Ala Ala Leu Gly Leu 580 585		
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	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
	50						55					60					
5	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
10					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
15	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
				115					120					125			
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
20							135										
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
25					150					155						160	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
30	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
35				195				200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
40					215								220				
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
					230					235					240		
45	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
50				260				265					270				
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
				275				280					285				
55	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	

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	290		295		300												
5	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
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	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
10					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
15	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
20		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
25		385				390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
35			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
40	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
45					485					490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
50				500					505					510			
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Ala	Lys	Gln	Thr	Ala	
			515					520					525				
55	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
	530						535					540					

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Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
 545 550 555 560

5 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
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10 Ala Ala Ser Gln Ala Ala Leu Gly Leu
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25 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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30 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60

35 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

40 Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

45 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
 100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
 115 120 125

50 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
 130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
 145 150 155 160

55 Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala

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	165	170	175
5	Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser 180 185 190		
10	Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu 195 200 205		
15	Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro 210 215 220		
20	Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys 225 230 235 240		
25	Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp 245 250 255		
30	Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser 260 265 270		
35	Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His 275 280 285		
40	Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser 290 295 300		
45	Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala 305 310 315 320		
50	Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg 325 330 335		
55	Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr 340 345 350		
	Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu 355 360 365		
	Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro 370 375 380		
	Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu 385 390 395 400		
	Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro 405 410 415		

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	Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys	420	425	430
5	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys	435	440	445
10	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His	450	455	460
15	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser	465	470	475
20	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr	485	490	495
25	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp	500	505	510
30	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Ala Ala	515	520	525
35	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu	530	535	540
40	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys	545	550	555
45	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val	565	570	575
50	Ala Ala Ser Gln Ala Ala Leu Gly Leu	580	585	
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	Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln	20	25	30
	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu			

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	35					40					45					
5	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
	50						55					60				
10	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
	65					70					75					80
15	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
20	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu
				100					105					110		
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
30	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
	130						135					140				
35	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145					150					155					160
40	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	
45	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser
				180					185					190		
50	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
55	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
		210					215					220				
60	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys
	225					230					235					240
65	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
					245					250					255	
70	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser
				260					265					270		
75	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His
			275					280					285			

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	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
5	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
10					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
15	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
20		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
25	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
35			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
40	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
45				485						490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
50				500					505					510			
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
55	Leu	Val	His	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
	530						535					540					

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Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
 545 550 555 560

5 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
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10 Ala Ala Ser Gln Ala Ala Leu Gly Leu
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Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
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25 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
 20 25 30

30 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

35 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

40 Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

45 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Lys Leu
 100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
 115 120 125

50 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
 130 135 140

55 Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
 145 150 155 160

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	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
5	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
10			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
15	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
20					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
25	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
30		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
35	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
40	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
45			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
50	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
55				405						410					415		

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Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

5 Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

10 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

15 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

20 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

25 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

30 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

35 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

40 Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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45 <213> Artificial sequence

<220>
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50 <400> 55

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
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55 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

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	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
			35					40					45				
5	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
10	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
15	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
20	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
30	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
35	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
40	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
45	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
50	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
55	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
60	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
65	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
70	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
75	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				

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	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
5	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
10					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
15	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
20		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
25	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
30	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Lys	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
35			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
40	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
45					485					490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
50				500					505					510			
	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
55	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
	530						535					540					

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Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
 545 550 555 560

 5 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
 565 570 575

 10 Ala Ala Ser Gln Ala Ala Leu Gly Leu
 580 585

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 15 <213> Artificial sequence

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 Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
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 25 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
 20 25 30

 30 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
 35 40 45

 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
 50 55 60
 35

 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
 65 70 75 80

 40 Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
 85 90 95

 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
 100 105 110
 45

 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
 115 120 125
 50

 Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
 130 135 140

 55 Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
 145 150 155 160

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	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
5	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
10			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
15	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
20					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
25	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
30		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
35	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
40	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
45			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
50	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
55				405						410					415		

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Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

5 Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

10 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

15 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

20 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

25 Leu Val Glu Leu Val Val His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

30 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

35 Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

40 Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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<212> PRT
45 <213> Artificial sequence

<220>
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55 Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

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	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
			35					40					45				
5	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
10	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
15	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
20	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
30	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
35	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
40	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
45	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
50	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
55	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
60	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
65	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
70	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
75	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				

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	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
5	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
10	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330						335	
15	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345						350		
20	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
25	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370				375						380					
30	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
35	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405					410						415		
40	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
45	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
50	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
	450					455					460						
55	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470				475						480	
60	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485					490						495		
65	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	Asp	Ala	Asp	
				500					505					510			
70	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
		515				520							525				
75	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	

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	530		535		540	
5	Lys 545	Ala Val Met Asp	Asp Phe Ala Ala Phe	Val Glu Lys Cys Cys Lys 555		
10		Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val 565		570	575	
15		Ala Ala Ser Gln Ala Ala Leu Gly Leu 580		585		
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25		<220> <223> HSA A569S <400> 58				
30		Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu 1 5 10 15				
35		Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln 20 25 30				
40		Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu 35 40 45				
45		Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys 50 55 60				
50		Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu 65 70 75 80				
55		Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro 85 90 95				
		Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu 100 105 110				
		Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His 115 120 125				
		Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg 130 135 140				
		Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg 145 150 155 160				

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	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
5	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
10			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
15	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
20					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
25				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
30	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
35	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
40					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
45	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
50		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
55	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	

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	405	410	415
5	Gln Val Ser Thr Pro Thr Leu Val	Glu Val Ser Arg Asn Leu Gly Lys	
	420	425	430
10	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys		
	435	440	445
15	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His		
	450	455	460
20	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser		
	465	470	475
25	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr		
	485	490	495
30	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp		
	500	505	510
35	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala		
	515	520	525
40	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu		
	530	535	540
45	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys		
	545	550	555
50	Ala Asp Asp Lys Glu Thr Cys Phe Ser Glu Glu Gly Lys Lys Leu Val		
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55	Ala Ala Ser Gln Ala Ala Leu Gly Leu		
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			15
	Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln		
	20	25	30

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	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
			35					40					45				
5	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
10	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
15	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
20	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Ala	Asn	Pro	Asn	Leu	
				100					105					110			
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
30	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
35	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
40	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
45	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
50	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
55	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
60	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
65	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
70	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
75	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	

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	275		280		285
5	Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser	290	295	300	
10	Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala	305	310	315	320
15	Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg	325	330	335	
20	Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr	340	345	350	
25	Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu	355	360	365	
30	Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro	370	375	380	
35	Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu	385	390	395	400
40	Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro	405	410	415	
45	Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys	420	425	430	
50	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys	435	440	445	
55	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His	450	455	460	
	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser	465	470	475	480
	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr	485	490	495	
	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp	500	505	510	
	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala	515	520	525	

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	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu
	530						535					540				
5	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys
	545					550					555					560
	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Leu	Val
10					565					570					575	
	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu							
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	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln
30				20					25					30		
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
			35					40					45			
35	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
	50						55					60				
	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
40	65					70					75					80
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
45	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asp	Leu
				100					105					110		
	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
50			115					120					125			
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
	130						135					140				
55	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg

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	145		150		155		160									
5	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	
10	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser
				180					185					190		
15	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
20	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
		210					215					220				
25	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys
	225					230					235					240
30	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
					245					250					255	
35	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser
				260					265					270		
40	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His
			275					280					285			
45	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser
		290					295					300				
50	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala
	305					310					315					320
55	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg
					325					330					335	
60	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr
				340					345					350		
65	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu
			355					360					365			
70	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro
		370					375					380				
75	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu
	385					390					395					400

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	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
5	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
10			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
15	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
20				485						490					495		
	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
25	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	
			515					520					525				
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
30		530					535					540					
	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
35	545					550					555					560	
	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
					565					570					575		
40	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu								
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55	1				5					10					15		
	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	

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	20					25					30					
5	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
			35					40					45			
10	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
		50					55					60				
15	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
	65				70						75					80
20	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
25	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Gly	Leu
				100					105					110		
30	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
35	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
		130					135					140				
40	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145						150					155				160
45	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	
50	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser
				180					185					190		
55	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
60	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
		210					215					220				
65	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys
	225						230					235				240
70	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
					245					250					255	
75	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser
				260					265					270		

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	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	275	280	285
5	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	290	295	300
10	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	305	310	315
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	325	330	335
15	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	340	345	350
20	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	355	360	365
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	370	375	380
25	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	385	390	395
30	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	405	410	415
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	420	425	430
35	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	435	440	445
40	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	450	455	460
45	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	465	470	475
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	485	490	495
50	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	500	505	510
55	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	515	520	525

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	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu	
	530						535					540					
5	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys	
	545					550					555					560	
	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val	
10					565					570					575		
	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu								
				580					585								
15																	
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	1				5					10					15		
	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	
30				20					25					30			
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
35			35					40					45				
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
40	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
45					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	His	Leu	
50				100					105					110			
	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
55	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
	130						135					140					

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	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
5	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
10				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
15	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
	210						215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
20	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
25					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
30	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
35		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
40	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
45				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
50			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
55	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	

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Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
 405 410 415
 5 Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
 420 425 430
 10 Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
 435 440 445
 15 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
 450 455 460
 20 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
 465 470 475 480
 25 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
 485 490 495
 30 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
 500 505 510
 35 Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
 515 520 525
 40 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
 530 535 540
 45 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
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	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	
				20					25					30			
5	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
			35					40					45				
10	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
15	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
20	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
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35	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
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40	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
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45	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
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50	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
55	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
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		210					215					220					
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	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
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		290					295					300					
10	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
15	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
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20	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
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25	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
30	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
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	385					390					395					400	
40	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
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45	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Ala	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
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60	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
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65	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
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70	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
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40	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
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45	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
50	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
55	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
60	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
65	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
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70	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
	130						135					140					

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	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
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					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
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	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
15	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
	210						215					220					
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	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
25					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
30	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
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	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
40	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
45				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
50			355					360					365				
	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
55	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	

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 5 Gln Val Ser Thr Pro Thr Leu Val Ala Val Ser Arg Asn Leu Gly Lys
 420 425 430
 10 Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
 435 440 445
 15 Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
 450 455 460
 20 Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
 465 470 475 480
 25 Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
 485 490 495
 30 Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
 500 505 510
 35 Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
 515 520 525
 40 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
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 45 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
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5	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
			35					40					45			
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
10		50					55					60				
	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
	65					70					75					80
15	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu
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	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
25			115					120					125			
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
	130						135					140				
30	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145					150					155					160
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
35					165					170					175	
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser
			180						185					190		
40	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
45	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
	210						215					220				
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50	225					230					235					240
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
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55	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser
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	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
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5	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
10	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
15	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
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25	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
30	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
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40	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
					405					410					415		
45	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
50	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
55	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
60	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475					480	
65	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
					485					490					495		
70	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Gln	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			
75	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala	

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	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys
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10	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val
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	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
35			35					40					45			
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
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	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
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				100					105						110	
50	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
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	130						135					140				

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	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
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10	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
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		210					215					220					
25	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
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30	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
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35	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
40	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
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45	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
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50	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
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55	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
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60	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
65	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
70	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
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75	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	

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10	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys
				420					425					430		
15	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys
			435					440					445			
20	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His
		450					455					460				
25	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser
	465					470					475					480
30	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr
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35	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp
				500					505					510		
40	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Met	Ala
			515					520					525			
45	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu
	530					535						540				
50	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys
	545				550						555					560
55	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val
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10	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
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15	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
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20	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
					85					90					95		
25	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Glu	Leu	
				100					105					110			
30	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
35	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
		130					135					140					
40	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
45	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
				165						170					175		
50	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
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		210					215					220					
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	225					230					235					240	
70	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
				245						250					255		
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	260	265	270
5	Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His 275 280 285		
10	Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser 290 295 300		
15	Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala 305 310 315 320		
20	Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg 325 330 335		
25	Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr 340 345 350		
30	Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu 355 360 365		
35	Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro 370 375 380		
40	Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu 385 390 395 400		
45	Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro 405 410 415		
50	Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys 420 425 430		
55	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys 435 440 445		
	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His 450 455 460		
	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser 465 470 475 480		
	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr 485 490 495		
	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp 500 505 510		

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	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala	
	515	520 525
5	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu	
	530	535 540
10	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys	
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		20 25 30
40	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu	
		35 40 45
45	Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys	
		50 55 60
50	Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu	
		65 70 75 80
55	Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro	
		85 90 95
	Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Glu Leu	
		100 105 110
	Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His	
		115 120 125
	Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg	

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	130		135		140												
5	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
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	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
10					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
15	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
20		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
25																	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
30	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
35			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
	290						295					300					
40																	
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
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45	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
50				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
55	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
	370						375					380					

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	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	385	390	395	400
5	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro		405	410	415
10	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys		420	425	430
	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys		435	440	445
15	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His		450	455	460
20	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser		465	470	475
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr			485	490
25	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp		500	505	510
30	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala		515	520	525
	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu		530	535	540
35	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys		545	550	555
40	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Pro	Lys	Leu	Val		565	570	575
45	Ala	Ala	Ser	Gln	Ala	Ala	Leu	Gly	Leu									580	585	
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5	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln
				20					25					30		
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu
			35					40					45			
10																
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys
		50					55					60				
15																
	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu
	65					70					75					80
20	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro
					85					90					95	
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Lys	Pro	Asn	Leu
				100					105					110		
25																
	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His
			115					120					125			
30	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg
		130					135					140				
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg
	145					150					155					160
35																
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala
					165					170					175	
40	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser
				180					185					190		
45	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu
			195					200					205			
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro
		210					215					220				
50																
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys
	225					230					235					240
55	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp
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	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
5	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
10		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
15	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
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	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
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	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
25	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
30		385				390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
35				405						410					415		
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
40	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
45		450					455					460					
	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
50		465				470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485						490					495		
55	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			

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Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

5 Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

10 Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
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Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

15 Ala Ala Ser Gln Ala Ala Leu Gly Leu
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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35 Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

40 Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

45 Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

50 Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Glu Asn Pro Asn Leu
100 105 110

55 Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

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	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
	130						135					140					
5	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
10					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
15	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
20		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
25	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
30	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
35			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
40	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
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	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
45					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
50				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
55	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					

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	Gln Asn Leu Ile Lys	Gln Asn Cys Glu Leu Phe	Glu Gln Leu Gly Glu
	385	390	395 400
5	Tyr Lys Phe Gln Asn Ala Leu Leu Val	Arg Tyr Thr Lys Lys Val Pro	
		405 410	415
10	Gln Val Ser Thr Pro Thr Leu Val	Glu Val Ser Arg Asn Leu Gly Lys	
		420 425	430
15	Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys		
		435 440	445
20	Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His		
		450 455	460
25	Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser		
		465 470	475 480
30	Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr		
		485 490	495
35	Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp		
		500 505	510
40	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala		
		515 520	525
45	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu		
		530 535	540
50	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys		
		545 550	555 560
55	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val		
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60	Ala Ala Ser Gln Ala Ala Leu Gly Leu		
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				20					25					30			
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
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	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
15	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Asn	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
20					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
30		130					135					140					
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
35	145					150					155					160	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
				165						170					175		
40	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
45			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
50	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
55					245					250					255		

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	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
5	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
10		290					295					300					
	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
15	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
20				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
25	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
30		385				390					395					400	
	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
35				405						410					415		
	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
40	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
45		450					455					460					
	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
50		465				470					475				480		
	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485						490					495		
55	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	
				500					505					510			

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	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala	
	515	520 525
5	Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu	
	530	535 540
10	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys	
	545	550 555 560
15	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val	
		565 570 575
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		20 25 30
45	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu	
		35 40 45
50	Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys	
		50 55 60
55	Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu	
		65 70 75 80
	Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro	
		85 90 95
	Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu	
		100 105 110
	Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His	
		115 120 125

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	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
	130						135					140					
5	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
10					165					170					175		
	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
15	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
20		210					215					220					
	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
25	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
30				260					265					270			
	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
35			275					280					285				
	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
40	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
45					325					330					335		
	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
50				340					345					350			
	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
55	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					

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	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	385	390	395	400
5	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro		405	410	415
10	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys		420	425	430
15	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys		435	440	445
20	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His		450	455	460
25	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser		465	470	475
30	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr		485	490	495
35	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp		500	505	510
40	Ile	Cys	Thr	Leu	Ser	Glu	Lys	Glu	Arg	Gln	Ile	Lys	Lys	Gln	Thr	Ala		515	520	525
45	Leu	Val	Glu	Leu	Val	Lys	His	Lys	Pro	Lys	Ala	Thr	Lys	Glu	Gln	Leu		530	535	540
50	Lys	Ala	Val	Met	Asp	Asp	Phe	Ala	Ala	Phe	Val	Glu	Lys	Cys	Cys	Lys		545	550	555
55	Ala	Asp	Asp	Lys	Glu	Thr	Cys	Phe	Ala	Glu	Glu	Gly	Lys	Lys	Phe	Val		565	570	575
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5	Glu	Asn	Phe	Lys	Ala	Leu	Val	Leu	Ile	Ala	Phe	Ala	Gln	Tyr	Leu	Gln	
				20					25					30			
	Gln	Cys	Pro	Phe	Glu	Asp	His	Val	Lys	Leu	Val	Asn	Glu	Val	Thr	Glu	
10			35					40					45				
	Phe	Ala	Lys	Thr	Cys	Val	Ala	Asp	Glu	Ser	Ala	Glu	Asn	Cys	Asp	Lys	
		50					55					60					
15	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Thr	Val	Ala	Thr	Leu	
	65					70					75					80	
	Arg	Glu	Thr	Tyr	Gly	Glu	Met	Ala	Asp	Cys	Cys	Ala	Lys	Gln	Glu	Pro	
20					85					90					95		
	Glu	Arg	Asn	Glu	Cys	Phe	Leu	Gln	His	Lys	Asp	Asp	Asn	Pro	Asn	Leu	
				100					105					110			
25	Pro	Arg	Leu	Val	Arg	Pro	Glu	Val	Asp	Val	Met	Cys	Thr	Ala	Phe	His	
			115					120					125				
	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
30		130					135					140					
	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
35	145					150					155					160	
	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
				165						170					175		
40	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
45			195					200					205				
	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
50	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
55					245					250					255		

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	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
5	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
10	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
15	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
20	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
25	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
30	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
35	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	
		370					375					380					
40	Gln	Asn	Leu	Ile	Lys	Gln	Asn	Cys	Glu	Leu	Phe	Glu	Gln	Leu	Gly	Glu	
	385					390					395					400	
45	Tyr	Lys	Phe	Gln	Asn	Ala	Leu	Leu	Val	Arg	Tyr	Thr	Lys	Lys	Val	Pro	
				405						410					415		
50	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Val	Ser	Arg	Asn	Leu	Gly	Lys	
				420					425					430			
55	Val	Gly	Ser	Lys	Cys	Cys	Lys	His	Pro	Glu	Ala	Lys	Arg	Met	Pro	Cys	
			435					440					445				
60	Ala	Glu	Asp	Tyr	Leu	Ser	Val	Val	Leu	Asn	Gln	Leu	Cys	Val	Leu	His	
		450					455					460					
65	Glu	Lys	Thr	Pro	Val	Ser	Asp	Arg	Val	Thr	Lys	Cys	Cys	Thr	Glu	Ser	
	465					470					475				480		
70	Leu	Val	Asn	Arg	Arg	Pro	Cys	Phe	Ser	Ala	Leu	Glu	Val	Asp	Glu	Thr	
				485						490					495		
75	Tyr	Val	Pro	Lys	Glu	Phe	Asn	Ala	Glu	Thr	Phe	Thr	Phe	His	Ala	Asp	

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	500	505	510
5	Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala 515 520 525		
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15	Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys 545 550 555 560		
20	Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val 565 570 575		
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50	Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu 35 40 45		
55	Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys 50 55 60		
60	Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu 65 70 75 80		
65	Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro 85 90 95		
70	Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Gln Leu 100 105 110		
75	Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His 115 120 125		

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	Asp	Asn	Glu	Glu	Thr	Phe	Leu	Lys	Lys	Tyr	Leu	Tyr	Glu	Ile	Ala	Arg	
	130						135					140					
5	Arg	His	Pro	Tyr	Phe	Tyr	Ala	Pro	Glu	Leu	Leu	Phe	Phe	Ala	Lys	Arg	
	145					150					155					160	
10	Tyr	Lys	Ala	Ala	Phe	Thr	Glu	Cys	Cys	Gln	Ala	Ala	Asp	Lys	Ala	Ala	
					165					170					175		
15	Cys	Leu	Leu	Pro	Lys	Leu	Asp	Glu	Leu	Arg	Asp	Glu	Gly	Lys	Ala	Ser	
				180					185					190			
20	Ser	Ala	Lys	Gln	Arg	Leu	Lys	Cys	Ala	Ser	Leu	Gln	Lys	Phe	Gly	Glu	
			195					200					205				
25	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Arg	Phe	Pro	
		210					215					220					
30	Lys	Ala	Glu	Phe	Ala	Glu	Val	Ser	Lys	Leu	Val	Thr	Asp	Leu	Thr	Lys	
	225					230					235					240	
35	Val	His	Thr	Glu	Cys	Cys	His	Gly	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	
					245					250					255		
40	Arg	Ala	Asp	Leu	Ala	Lys	Tyr	Ile	Cys	Glu	Asn	Gln	Asp	Ser	Ile	Ser	
				260					265					270			
45	Ser	Lys	Leu	Lys	Glu	Cys	Cys	Glu	Lys	Pro	Leu	Leu	Glu	Lys	Ser	His	
			275					280					285				
50	Cys	Ile	Ala	Glu	Val	Glu	Asn	Asp	Glu	Met	Pro	Ala	Asp	Leu	Pro	Ser	
		290					295					300					
55	Leu	Ala	Ala	Asp	Phe	Val	Glu	Ser	Lys	Asp	Val	Cys	Lys	Asn	Tyr	Ala	
	305					310					315					320	
60	Glu	Ala	Lys	Asp	Val	Phe	Leu	Gly	Met	Phe	Leu	Tyr	Glu	Tyr	Ala	Arg	
					325					330					335		
65	Arg	His	Pro	Asp	Tyr	Ser	Val	Val	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Thr	
				340					345					350			
70	Tyr	Glu	Thr	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Ala	Ala	Asp	Pro	His	Glu	
			355					360					365				
75	Cys	Tyr	Ala	Lys	Val	Phe	Asp	Glu	Phe	Lys	Pro	Leu	Val	Glu	Glu	Pro	

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	370					375					380					
5	Gln 385	Asn	Leu	Ile	Lys	Gln 390	Asn	Cys	Glu	Leu	Phe 395	Glu	Gln	Leu	Gly	Glu 400
10	Tyr	Lys	Phe	Gln	Asn 405	Ala	Leu	Leu	Val	Arg 410	Tyr	Thr	Lys	Lys	Val 415	Pro
15	Gln	Val	Ser	Thr 420	Pro	Thr	Leu	Val	Glu 425	Val	Ser	Arg	Asn	Leu 430	Gly	Lys
20	Val	Gly	Ser 435	Lys	Cys	Cys	Lys	His 440	Pro	Glu	Ala	Lys	Arg 445	Met	Pro	Cys
25	Ala	Glu 450	Asp	Tyr	Leu	Ser	Val 455	Val	Leu	Asn	Gln	Leu 460	Cys	Val	Leu	His
30	Glu 465	Lys	Thr	Pro	Val	Ser 470	Asp	Arg	Val	Thr	Lys 475	Cys	Cys	Thr	Glu	Ser 480
35	Leu	Val	Asn	Arg	Arg 485	Pro	Cys	Phe	Ser	Ala 490	Leu	Glu	Val	Asp	Glu 495	Thr
40	Tyr	Val	Pro	Lys 500	Glu	Phe	Asn	Ala	Glu 505	Thr	Phe	Thr	Phe	His 510	Ala	Asp
45	Ile	Cys	Thr 515	Leu	Ser	Glu	Lys	Glu 520	Arg	Gln	Ile	Lys	Lys 525	Gln	Thr	Ala
50	Leu	Val 530	Glu	Leu	Val	Lys	His 535	Lys	Pro	Lys	Ala	Thr 540	Lys	Glu	Gln	Leu
55	Lys 545	Ala	Val	Met	Asp	Asp 550	Phe	Ala	Ala	Phe	Val 555	Glu	Lys	Cys	Cys	Lys 560
60	Ala	Asp	Asp	Lys	Glu 565	Thr	Cys	Phe	Ala	Glu 570	Glu	Gly	Pro	Lys	Leu 575	Val
65	Ala	Ala	Ser	Gln 580	Ala	Ala	Leu	Gly	Leu 585							

Claims

- 55 1. A polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or a fragment thereof, which polypeptide has one or more alterations in Domain I of the albumin, fragment or fusion polypeptide and has one or more alterations in Domain III of the albumin, fragment or fusion polypeptide and has an increased binding affinity to FcRn and/or longer plasma half-life compared with the binding affinity of a parent

albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof to FcRn wherein the alteration(s) in Domain I are selected from positions corresponding to any of positions 78 to 120 of SEQ ID NO: 2 and the alteration(s) in Domain III are selected from positions corresponding to any of positions 425, 505, 510, 512, 524, 527, 531, 534, 569, 573, 575 of SEQ ID NO: 2.

2. The polypeptide according to claim 1, wherein the sequence identity of the polypeptide to SEQ ID NO: 2 is more than 95%, more preferred more than 96%, even more preferred more than 97%, more preferred more than 98% and most preferred more than 99%.
3. The polypeptide according to claim 1 or 2 wherein the one or more alterations in Domain I are selected from positions corresponding to any of positions from 78 to 88 and/or from any of 105 to 120 of SEQ ID NO: 2.
4. The polypeptide according to claim 1, 2 or 3 comprising alterations at positions corresponding to positions (a) 83 and 573; (b) 111 and 573; (c) 83 and 111; (d) 82 and 83; (e) 82 and 111; (f) 82 and 112; (g) 82 and 573; (h) 83 and 112; (i) 111 and 112; (j) 83, 111, and 573; (k) 112 and 573; (l) 82, 83, and 111; (m) 82, 83, and 112; (n) 82, 83, and 573; (o) 82, 111, and 112; (p) 82, 111, and 573; (q) 82, 112, and 573; (r) 83, 111, and 112; (s) 83, 112, and 573; (t) 111, 112, and 573; (u) 82, 83, 111, and 112; (v) 82, 83, 111, and 573; (w) 82, 83, 112, and 573; (x) 82, 111, 112, and 573; (y) 83, 111, 112, and 573; or (z) 82, 83, 111, 112, and 573 of SEQ ID NO: 2.
5. The polypeptide according to any of claims 1 to 4 comprising alterations at positions corresponding to positions 83 and 573 of SEQ ID NO: 2.
6. The polypeptide according to any of claims 1 to 5 comprising alterations at positions corresponding to positions 111 and 573 of SEQ ID NO: 2.
7. The polypeptide according to any of claims 1 to 6 comprising alterations at positions corresponding to positions 83 and 111 of SEQ ID NO: 2.
8. The polypeptide according to any of claims 1 to 7 wherein the alteration in Domain I and/or the alteration in Domain III is a substitution.
9. The polypeptide of any of claims 1 to 8 wherein the alteration at the position corresponding to position 83 is a substitution to N, K or S,
10. The polypeptide of any of claims 1 to 9 wherein the alteration at the position corresponding to position 111 is a substitution to D, G, H, R, Q or E.
11. The polypeptide of any of claims 1 to 10 wherein the alteration at the position corresponding to position 573 is a substitution to a P, Y, W, H, F, T, I or V, preferably to P, Y or W, more preferably to P.
12. The polypeptide of any of claims 1 to 11 wherein the reference albumin is HSA (SEQ ID No: 2) or a fragment thereof, or a fusion polypeptide comprising HSA or a fragment thereof, most preferably SEQ ID NO: 2.
13. The polypeptide according to any of claims 1 to 12, having a stronger binding affinity to FcRn and/or longer plasma half-life than a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof.
14. A fusion polypeptide comprising a polypeptide according to any of claims 1 to 13 and a fusion partner polypeptide selected from a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.
15. A method for preparing a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof having a binding affinity to FcRn which is increased compared to the binding affinity of a reference albumin, fragment or fusion thereof to FcRn and/or a plasma half-life that is increased compared to the plasma half-life of a reference albumin, fragment or fusion thereof to FcRn, comprising:
 - (a) Providing a nucleic acid encoding a parent albumin having at least 80% sequence identity to SEQ ID NO: 2;
 - (b) Modifying the nucleic acid sequence of step (a), to encode a polypeptide according to any of claims 1 to 14;
 - (c) optionally introducing the modified sequence of step (b) in a suitable host cell;

- (d) optionally growing the cells in a suitable growth medium under condition leading to expression of the polypeptide; and
- (e) optionally recovering the polypeptide from the growth medium.

- 5 **16.** A conjugate comprising a polypeptide according to any of claims 1 to 14 or obtainable by a method according to claim 15 and a conjugation partner, preferably to a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.
- 10 **17.** An associate comprising a polypeptide according to any of claims 1 to 14 or obtainable by a method according to claim 15 and a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.
- 18.** A nanoparticle or microparticle comprising a polypeptide according to any of claims 1 to 14 or obtainable by a method according to claim 15, a conjugate according to claim 16 or an associate according to claim 17.
- 15 **19.** A composition comprising a polypeptide according to any of claims 1 to 14 or obtainable by a method according to claim 15, a conjugate according to claim 16, an associate according to claim 17 or a nanoparticle or microparticle according claim 18, wherein the binding affinity of the polypeptide, fusion polypeptide, conjugate, associate or nanoparticle or microparticle to FcRn is stronger than the binding affinity of a composition comprising the corresponding parent albumin, reference albumin, fragment thereof or fusion polypeptide, conjugate, associate or nanoparticle or microparticle comprising said parent albumin, reference albumin or fragment or fusion thereof to FcRn.
- 20 **20.** A composition according to claim 19 where the binding affinity of the polypeptide, fusion polypeptide, conjugate, associate or nanoparticle or microparticle to FcRn is stronger than the binding affinity of HSA to FcRn.
- 25 **21.** A composition according to claim 19 or 20, wherein the binding coefficient of the variant to the polypeptide, fusion polypeptide, conjugate, associate or nanoparticle or microparticle to FcRn is less than 0.9X KD of HSA to FcRn, more preferred less than 0.5X KD of HSA to FcRn, more preferred less than 0.1X KD of HSA to FcRn, even more preferred less than 0.05X KD of HSA to FcRn, even more preferred less than 0.02X KD of HSA to FcRn and most preferred less than 0.01X KD of HSA to FcRn.
- 30 **22.** The composition according to any of claims 19 to 21, comprising a polypeptide according to any of claims 1 to 14 or obtainable by a method according to claim 15, a conjugate according to claim 16, an associate according to claim 17 or a nanoparticle or microparticle according claim 18, further comprising a compound comprising an albumin binding domain (ABD) and a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.
- 35 **23.** The composition according to any of claims 19 to 23, comprising a pharmaceutically acceptable carrier or excipient.
- 24.** Use of a polypeptide according to any of claims 1 to 14 or obtainable by a method according to claim 15, a conjugate according to claim 16, an associate according to claim 17 or a nanoparticle or microparticle according claim 18 or a composition according to any of claims 19 to 23 to alter the binding affinity to FcRn or half-life, preferably in plasma, of a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.
- 40 **25.** A method for increasing the binding affinity to FcRn or half-life preferably in plasma, of a molecule comprising:
 - 45 (a) where the molecule is a polypeptide, fusing or conjugating the molecule to a polypeptide according to any of claims 1 to 14 or obtainable by the method of claim 15, or to a conjugate according to claim 16; associating the molecule to a polypeptide according to any of claims 1 to 14 or obtainable by the method of claim 15 or to a conjugate according to claim 16; incorporating the molecule in an associate according to claim 17, in a nanoparticle or microparticle according to claim 18 or a composition according to any of claims 19 to 23;
 - 50 (b) where the molecule is not a polypeptide, conjugating the molecule to a polypeptide according to any of claims 1 to 14 or obtainable by the method of claim 15, or to a conjugate according to claim 16; associating the molecule to a polypeptide according to any of claims 1 to 14 or obtainable by the method of claim 15 or to a conjugate according to claim 16; incorporating the molecule in an associate according to claim 17, in a nanoparticle or microparticle according to claim 18 or a composition according to any of claims 19 to 23.
- 55 **26.** A method according to claim 25 wherein the molecule is a therapeutic, prophylactic, diagnostic, imaging or other beneficial moiety.

27. A polypeptide, fusion polypeptide, conjugate, associate, nanoparticle or microparticle or composition thereof according to any of claims 1 to 14, 16 to 26 or obtainable by the method of claim 15 wherein the polypeptide, fusion polypeptide, conjugate, associate, nanoparticle or microparticle or composition comprises one or more moiety selected from:

(a) 4-1BB ligand, 5-helix, A human C-C chemokine, A human L105 chemokine, A human L105 chemokine designated huL105_3., A monokine induced by gamma-interferon (MIG), A partial CXCR4B protein, A platelet basic protein (PBP), α 1-antitrypsin, ACRP-30 Homologue; Complement Component C1q C, Adenoid-expressed chemokine (ADEC), aFGF; FGF-1, AGF, AGF Protein, albumin, an etoposide, angiostatin, Anthrax vaccine, Antibodies specific for collapsin, antistasin, Anti-TGF beta family antibodies, antithrombin III, APM-1; ACRP-30; Famoxin, apo-lipoprotein species, Arylsulfatase B, b57 Protein, BCMA, Beta-thromboglobulin protein (beta-TG), bFGF; FGF2, Blood coagulation factors, BMP Processing Enzyme Furin, BMP-10, BMP-12, BMP-15, BMP-17, BMP-18, BMP-2B, BMP-4, BMP-5, BMP-6, BMP-9, Bone Morphogenic Protein-2, calcitonin, Calpain-10a, Calpain-10b, Calpain-10c, Cancer Vaccine, Carboxypeptidase, C-C chemokine, MCP2, CCR5 variant, CCR7, CCR7, CD11a Mab, CD137; 4-1BB Receptor Protein, CD20 Mab, CD27, CD27L, CD30, CD30 ligand, CD33 immunotoxin, CD40, CD40L, CD52 Mab, Cerebus Protein, Chemokine Eotaxin., Chemokine hIL-8, Chemokine hMCP1, Chemokine hMCP1a, Chemokine hMCP1b, Chemokine hMCP2, Chemokine hMCP3, Chemokine hSDF1b, Chemokine MCP-4, chemokine TECK and TECK variant, Chemokine-like protein IL-8M1 Full-Length and Mature, Chemokine-like protein IL-8M10 Full-Length and Mature, Chemokine-like protein IL-8M3, Chemokine-like protein IL-8M8 Full-Length and Mature, Chemokine-like protein IL-8M9 Full-Length and Mature, Chemokine-like protein PF4-414 Full-Length and Mature, Chemokine-like protein PF4-426 Full-Length and Mature, Chemokine-like protein PF4-M2 Full-Length and Mature, Cholera vaccine, Chondromodulin-like protein, c-kit ligand; SCF; Mast cell growth factor; MGF; Fibrosarcoma-derived stem cell factor, CNTF and fragment thereof (such as CNTF α 15'(Axokine™)), coagulation factors in both pre and active forms, collagens, Complement C5 Mab, Connective tissue activating protein-III, CTAA16.88 Mab, CTAP-III, CTLA4-Ig, CTLA-8, CXC3, CXC3, CXCR3; CXC chemokine receptor 3, cyanovirin-N, Darbepoetin, designated exodus, designated huL105_7., DIL-40, DNase, EDAR, EGF Receptor Mab, ENA-78, Endostatin, Eotaxin, Epithelial neutrophil activating protein-78, EPO receptor; EPOR, erythropoietin (EPO) and EPO mimics, Eutropin, Exodus protein, Factor IX, Factor VII, Factor VIII, Factor X and Factor XIII, FAS Ligand Inhibitory Protein (DcR3), FasL, FasL, FasL, FGF, FGF-12; Fibroblast growth factor homologous factor-1, FGF-15, FGF-16, FGF-18, FGF-3; INT-2, FGF-4; gelonin, HST-1; HBGF-4, FGF-5, FGF-6; Heparin binding secreted transforming factor-2, FGF-8, FGF-9; Glia activating factor, fibrinogen, flt-1, flt-3 ligand, Follicle stimulating hormone Alpha subunit, Follicle stimulating hormone Beta subunit, Folliotropin, Fractalkine, fragment. myofibrillar protein Troponin I, FSH, Galactosidase, Galectin-4, G-CSF, GDF-1, Gene therapy, Glioma-derived growth factor, glucagon, glucagon-like peptides, Glucocerebrosidase, glucose oxidase, Glucosidase, Glycodelin-A; Progesterone-associated endometrial protein, GM-CSF, gonadotropin, Granulocyte chemotactic protein-2 (GCP-2), Granulocyte-macrophage colony stimulating factor, growth hormone, Growth related oncogene-alpha (GRO-alpha), Growth related oncogene-beta (GRO-beta), Growth related oncogene-gamma (GRO-gamma), hAPO-4; TROY, hCG, Hepatitis B surface Antigen, Hepatitis B Vaccine, HER2 Receptor Mab, hirudin, HIV gp120, HIV gp41, HIV Inhibitor Peptide, HIV Inhibitor Peptide, HIV Inhibitor Peptide, HIV protease inhibiting peptides, HIV-1 protease inhibitors, HPV vaccine, Human 6CKine protein, Human Act-2 protein, Human adipogenesis inhibitory factor, human B cell stimulating factor-2 receptor, Human beta-chemokine H1305 (MCP-2), Human C-C chemokine DGWCC, Human CC chemokine ELC protein, Human CC type chemokine interleukin C, Human CCC3 protein, Human CCF18 chemokine, Human CC-type chemokine protein designated SLC (secondary lymphoid chemokine), Human chemokine beta-8 short forms, Human chemokine C10, Human chemokine CC-2, Human chemokine CC-3, Human chemokine CCR-2, Human chemokine Ckbeta-7, Human chemokine ENA-78, Human chemokine eotaxin, Human chemokine GRO alpha, Human chemokine GROalpha, Human chemokine GRObeta, Human chemokine HCC-1, Human chemokine HCC-1, Human chemokine I-309, Human chemokine IP-10, Human chemokine L105_3, Human chemokine L105_7, Human chemokine MIG, Human chemokine MIG-beta protein, Human chemokine MIP-1alpha, Human chemokine MIP1beta, Human chemokine MIP-3alpha, Human chemokine MIP-3beta, Human chemokine PF4, Human chemokine protein 331D5, Human chemokine protein 61164, Human chemokine receptor CXCR3, Human chemokine SDF1alpha, Human chemokine SDF1beta, Human chemokine ZSIG-35, Human Chr19Kine protein, Human CKbeta-9, Human CKbeta-9, Human CX3C 111 amino acid chemokine, Human DNAX interleukin-40, Human DVic-1 C-C chemokine, Human EDIRF I protein sequence, Human EDIRF II protein sequence, Human eosinocyte CC type chemokine eotaxin, Human eosinophil-expressed chemokine (EEC), Human fast twitch skeletal muscle troponin C, Human fast twitch skeletal muscle troponin I, Human fast twitch skeletal muscle Troponin subunit C, Human fast twitch skeletal muscle Troponin subunit I Protein, Human fast twitch skeletal muscle Troponin subunit T, Human fast twitch skeletal muscle troponin T, Human foetal spleen ex-

pressed chemokine, FSEC, Human GM-CSF receptor, Human gro-alpha chemokine, Human gro-beta chemokine, Human gro-gamma chemokine, Human IL-16 protein, Human IL-1RD10 protein sequence, Human IL-1RD9, Human IL-5 receptor alpha chain, Human IL-6 receptor, Human IL-8 receptor protein hIL8RA, Human IL-8 receptor protein hIL8RB, Human IL-9 receptor protein, Human IL-9 receptor protein variant #3, Human IL-9 receptor protein variant fragment, Human IL-9 receptor protein variant fragment#3, Human interleukin 1 delta, Human Interleukin 10, Human Interleukin 10, Human interleukin 18, Human interleukin 18 derivatives, Human interleukin-1 beta precursor, Human interleukin-1 beta precursor., Human interleukin-1 receptor accessory protein, Human interleukin-1 receptor antagonist beta, Human interleukin-1 type-3 receptor, Human Interleukin-10 (precursor), Human Interleukin-10 (precursor), Human interleukin-11 receptor, Human interleukin-12 40 kD subunit, Human interleukin-12 beta-1 receptor, Human interleukin-12 beta-2 receptor, Human Interleukin-12 p35 protein, Human Interleukin-12 p40 protein, Human interleukin-12 receptor, Human interleukin-13 alpha receptor, Human interleukin-13 beta receptor, Human interleukin-15, Human interleukin-15 receptor from clone P1, Human interleukin-17 receptor, Human interleukin-18 protein (IL-18), Human interleukin-3, human interleukin-3 receptor, Human interleukin-3 variant, Human interleukin-4 receptor, Human interleukin-5, Human interleukin-6, Human interleukin-7, Human interleukin-7., Human interleukin-8 (IL-8), Human intracellular IL-1 receptor antagonist, Human IP-10 and HIV-1 gp120 hypervariable region fusion protein, Human IP-10 and human Muc-1 core epitope (VNT) fusion protein, human liver and activation regulated chemokine (LARC), Human Lkn-1 Full-Length and Mature protein, Human mammary associated chemokine (MACK) protein Full-Length and Mature, Human mature chemokine Ckbeta-7, Human mature gro-alpha, Human mature gro-gamma polypeptide used to treat sepsis, Human MCP-3 and human Muc-1 core epitope (VNT) fusion protein, Human MI10 protein, Human MI1A protein, Human monocyte chemoattractant factor hMCP-1, Human monocyte chemoattractant factor hMCP-3, Human monocyte chemotactic proprotein (MCP) sequence, Human neurotactin chemokine like domain, Human non-ELR CXC chemokine H174, Human non-ELR CXC chemokine IP10, Human non-ELR CXC chemokine Mig, Human PAI-1 mutants, Human protein with IL-16 activity, Human protein with IL-16 activity, Human secondary lymphoid chemokine (SLC), Human SISD protein, Human STCP-1, Human stromal cell-derived chemokine, SDF-1, Human T cell mixed lymphocyte reaction expressed chemokine (TMEC), Human thymus and activation regulated cytokine (TARC), Human thymus expressed, Human TNF-alpha, Human TNF-alpha, Human TNF-beta (LT-alpha), Human type CC chemokine eotaxin 3 protein sequence, Human type II interleukin-1 receptor, Human wild-type interleukin-4 (hIL-4) protein, Human ZCHEMO-8 protein, Humanized Anti-VEGF Antibodies, and fragments thereof, Humanized Anti-VEGF Antibodies, and fragments thereof, Hyaluronidase, ICE 10 kD subunit., ICE 20 kD subunit., ICE 22 kD subunit., Iduronate-2-sulfatase, Iduronidase, IL-1 alpha, IL-1 beta, IL-1 inhibitor (IL-1i), IL-1 mature, IL-10 receptor, IL-11, IL-11, IL-12 p40 subunit., IL-13, IL-14, IL-15, IL-15 receptor, IL-17, IL-17 receptor, IL-17 receptor, IL-17 receptor, IL-19, IL-1i fragments, IL1-receptor antagonist, IL-21 (TIF), IL-3 containing fusion protein., IL-3 mutant proteins, IL-3 variants, IL-3 variants, IL-4, IL-4 mutein, IL-4 mutein Y124G, IL-4 mutein Y124X, IL-4 muteins, IL-5 receptor, IL-6, IL-6 receptor, IL-7 receptor clone, IL-8 receptor, IL-9 mature protein variant (Met117 version), immunoglobulins or immunoglobulin-based molecules or fragment of either (e.g. a Small Modular ImmunoPharmaceutical™ ("SMIP") or dAb, Fab' fragments, F(ab')₂, scAb, scFv or scFv fragment), including but not limited to plasminogen, Influenza Vaccine, Inhibin alpha, Inhibin beta, insulin, insulin-like growth factor, Integrin Mab, inter-alpha trypsin inhibitor, inter-alpha trypsin inhibitor, Interferon gamma-inducible protein (IP-10), interferons (such as interferon alpha species and sub-species, interferon beta species and sub-species, interferon gamma species and sub-species), interferons (such as interferon alpha species and sub-species, interferon beta species and sub-species, interferon gamma species and sub-species), Interleukin 6, Interleukin 8 (IL-8) receptor, Interleukin 8 receptor B, Interleukin-1 alpha, Interleukin-2 receptor associated protein p43, interleukin-3, interleukin-4 muteins, Interleukin-8 (IL-8) protein., interleukin-9, Interleukin-9 (IL-9) mature protein (Thr117 version), interleukins (such as IL10, IL11 and IL2), interleukins (such as IL10, IL11 and IL2), Japanese encephalitis vaccine, Kalikrein Inhibitor, Keratinocyte growth factor, Kunitz domain protein (such as aprotinin, amyloid precursor protein and those described in WO 03/066824, with or without albumin fusions), Kunitz domain protein (such as aprotinin, amyloid precursor protein and those described in WO 03/066824, with or without albumin fusions), LACI, lactoferrin, Latent TGF-beta binding protein II, leptin, Liver expressed chemokine-1 (LVEC-1), Liver expressed chemokine-2 (LVEC-2), LT-alpha, LT-beta, Luteinization Hormone, Lyme Vaccine, Lymphotoxin, Macrophage derived chemokine analogue MDC (n+1), Macrophage derived chemokine analogue MDC-eyfy, Macrophage derived chemokine analogue MDC-yl, Macrophage derived chemokine, MDC, Macrophage-derived chemokine (MDC), Maspin; Protease Inhibitor 5, MCP-1 receptor, MCP-1a, MCP-1b, MCP-3, MCP-4 receptor, M-CSF, Melanoma inhibiting protein, Membrane-bound proteins, Met117 human interleukin 9, MIP-3 alpha, MIP-3 beta, MIP-Gamma, MIRAP, Modified Rantes, monoclonal antibody, MP52, Mutant Interleukin 6 S176R, myofibrillar contractile protein Troponin I, Natriuretic Peptide, Nerve Growth Factor-beta, Nerve Growth Factor-beta2, Neuropilin-1, Neuropilin-2, Neurotactin, Neurotrophin-3, Neurotrophin-4, Neurotrophin-4a, Neurotrophin-4b, Neurotrophin-

4c, Neurotrophin-4d, Neutrophil activating peptide-2 (NAP-2), NOGO-66 Receptor, NOGO-A, NOGO-B, NOGO-C, Novel beta-chemokine designated PTEC, N-terminal modified chemokine GroHEK/hSDF-1alpha, N-terminal modified chemokine GroHEK/hSDF-1beta., N-terminal modified chemokine met-hSDF-1 alpha, N-terminal modified chemokine met-hSDF-1 beta, OPGL, Osteogenic Protein-1; OP-1; BMP-7, Osteogenic Protein-2, OX40; ACT-4, OX40L, Oxytocin (Neurophysin I), parathyroid hormone, Patched, Patched-2, PDGF-D, Pertussis toxoid, Pituitary expressed chemokine (PGEC), Placental Growth Factor, Placental Growth Factor-2, Plasminogen Activator Inhibitor-1; PAI-1, Plasminogen Activator Inhibitor-2; PAI-2, Plasminogen Activator Inhibitor-2; PAI-2, Platelet derived growth factor, Platelet derived growth factor Bv-sis, Platelet derived growth factor precursor A, Platelet derived growth factor precursor B, Platelet Mab, platelet-derived endothelial cell growth factor (PD-ECGF), Platelet-Derived Growth Factor A chain, Platelet-Derived Growth Factor B chain, polypeptide used to treat sepsis, Preproapolipoprotein "milano" variant, Preproapolipoprotein "paris" variant, pre-thrombin, Primate CC chemokine "ILINCK", Primate CXC chemokine "IBICK", proinsulin, Prolactin, Prolactin2, prosaptide, Protease inhibitor peptides, Protein C, Protein S, pro-thrombin, prourokinase, RANTES, RANTES 8-68, RANTES 9-68, RANTES peptide, RANTES receptor, Recombinant interleukin-16, Resistin, restrictocin, Retroviral protease inhibitors, ricin, Rotavirus Vaccine, RSV Mab, saporin, sarcin, Secreted and Transmembrane polypeptides, Secreted and Transmembrane polypeptides, serum cholinesterase, serum protein (such as a blood clotting factor), Soluble BMP Receptor Kinase Protein-3, Soluble VEGF Receptor, Stem Cell Inhibitory Factor, Straphylococcus Vaccine, Stromal Derived Factor-1 alpha, Stromal Derived Factor-1 beta, Substance P (tachykinin), T1249 peptide, T20 peptide, T4 Endonuclease, TACI, Tarc, TGF-beta 1, TGF-beta 2, Thr117 human interleukin 9, thrombin, thrombopoietin, Thrombopoietin derivative1, Thrombopoietin derivative2, Thrombopoietin derivative3, Thrombopoietin derivative4, Thrombopoietin derivative5, Thrombopoietin derivative6, Thrombopoietin derivative7, Thymus expressed chemokine (TECK), Thyroid stimulating Hormone, tick anticoagulant peptide, Tim-1 protein, TNF-alpha precursor, TNF-R, TNF-RII; TNF p75 Receptor; Death Receptor, tPA, transferrin, transforming growth factor beta, Troponin peptides, Truncated monocyte chemotactic protein 2 (6-76), Truncated monocyte chemotactic protein 2 (6-76), Truncated RANTES protein (3-68), tumour necrosis factor, Urate Oxidase, urokinase, Vasopressin (Neurophysin II), VEGF R-3; flt-4, VEGF Receptor; KDR; flk-1, VEGF-110, VEGF-121, VEGF-138, VEGF-145, VEGF-162, VEGF-165, VEGF-182, VEGF-189, VEGF-206, VEGF-D, VEGF-E; VEGF-X, von Willebrand's factor, Wild type monocyte chemotactic protein 2, Wild type monocyte chemotactic protein 2, ZTGF-beta 9, alternative antibody scaffolds e.g. anticalin(s), adnectin(s), fibrinogen fragment(s), nanobodies such as camelid nanobodies, infestin, and/or any of the molecules mentioned in WO01/79271 (particularly page 9 and/or Table 1), WO 2003/59934 (particularly Table 1), WO03/060071 (particularly Table 1) or WO01/079480 (particularly Table 1) (each incorporated herein by reference in their entirety),

(b) chemotherapy drugs such as: 13-cis-Retinoic Acid, 2-CdA, 2-Chlorodeoxyadenosine, 5-Azacididine, 5-Fluorouracil, 5-FU, 6-Mercaptopurine, 6-MP, 6-TG, 6-Thioguanine, A, Abraxane, Accutane®, Actinomycin-D, Adriamycin®, Aducril®, Agrylin®, Ala-Cort®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ®, Alkeran®, All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron®, Anastrozole, Arabinosylcytosine, Ara-C, Aranesp®, Aredia®, Arimidex®, Aromasin®, Arranon®, Arsenic Trioxide, Asparaginase, ATRA, Avastin®, Azacididine, BCG, BCNU, Bevacizumab, Bexarotene, BEXXAR®, Bicalutamide, BiCNU, Bleomycin, Bortezomib, Busulfan, Busulfex®, C225, Calcium Leucovorin, Campath®, Camptosar®, Camptothecin-11, Capecitabine, Carac™, Carboplatin, Carmustine, Carmustine Wafer, Casodex®, CC-5013, CCNU, CDDP, CeeNU, Cerubidine®, Cetuximab, Chlorambucil, Cisplatin, Citrovorum Factor, Cladribine, Cortisone, Cosmegen®, CPT-11, Cyclophosphamide, Cyadren®, Cytarabine, Cytarabine Liposomal, Cytosar-U®, Cytosan®, Dacarbazine, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome®, Decadron, Decitabine, Delta-Cortef®, Deltasone®, Denileukin diftitox, DepoCyt™, Dexamethasone, Dexamethasone acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodex, Docetaxel, Doxil®, Doxorubicin, Doxorubicin liposomal, Droxia™, DTIC, DTIC-Dome®, Duralone®, Efudex®, Eligard™, Ellence™, Eloxatin™, Elspar®, Emcynt®, Epirubicin, Epoetin alfa, Erbitux™, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethylol, Etopophos®, Etoposide, Etoposide Phosphate, Eulexin®, Evista®, Exemestane, Fareston®, Faslodex®, Femara®, Filgrastim, Floxuridine, Fludara®, Fludarabine, Fluoroplex®, Fluorouracil, Fluorouracil (cream), Fluoxymesterone, Flutamide, Folinic Acid, FUDR®, Fulvestrant, G-CSF, Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Gemzar®, Gleevec™, Gliadel® Wafer, GM-CSF, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Halotestin®, Herceptin®, Hexadrol, Hexalen®, Hexamethylmelamine, HMM, Hycamtin®, Hydrea®, Hydrocort Acetate®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab Tiuxetan, Idamycin®, Idarubicin, Ifex®, IFN-alpha, Ifosfamide, Interleukin-2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa®, Irinotecan, Isotretinoin, Kidrolase®, Lana-

cort®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine™, Leuprolide, Leurocristine, Leustatin™, Liposomal Ara-C, Liquid Pred®, Lomustine, L-PAM, L-Sarcosyl, Lupron®, Lupron Depot®, M, Matulane®, Maxidex, Mechlorethamine, Mechlorethamine Hydrochloride, Medralone®, Medrol®, Megace®, Megestrol, Megestrol Acetate, Melphalan, Mercaptopurine, Mesna, Mesnex™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticorten®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol®, MTC, MTX, Mustargen®, Mustine, Mutamycin®, Myleran®, Mylocel™, Mylotarg®, Navelbine®, Nelarabine, Neosar®, Neulasta™, Neumega®, Neupogen®, Nexavar®, Nilandron®, Nilutamide, Nipent®, Nitrogen Mustard, Novaldex®, Novantrone®, Octreotide, Octreotide acetate, Oncospar®, Oncovin®, Ontak®, Onxal™, Oprevelkin, Orapred®, Orasone®, Oxaliplatin, a taxol or taxol derivative e.g. Paclitaxel or Paclitaxel Protein-bound, Pamidronate, Panitumumab, Panretin®, Paraplatin®, Pediapred®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON™, PEG-L-asparaginase, PEMETREXED, Pentostatin, Phenylalanine Mustard, Platinol®, Platinol-AQ®, Prednisolone, Prednisone, Prelone®, Procarbazine, PROCIT®, Proleukin®, Prolifeprospan 20 with Carmustine Implant, Purinethol®, R, Raloxifene, Revlimid®, Rheumatrex®, Rituxan®, Rituximab, Roferon-A® (Interferon Alfa-2a), Rubex®, Rubidomycin hydrochloride, Sandostatin®, Sandostatin LAR®, Sargramostim, Solu-Cortef®, Solu-Medrol®, Sorafenib, SPRYCEL™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent®, Tamoxifen, Tarceva®, Targretin®, Taxol®, Taxotere®, Temodar®, Temozolomide, Teniposide, TESPA, Thalidomide, Thalomid®, TheraCys®, Thioguanine, Thioguanine Tabloid®, Thiophosphoamide, Thioplex®, Thiotepa, TICE®, Toposar®, Topotecan, Toremifene, Tositumomab, Trastuzumab, Tretinoin, Trexall™, Trisenox®, TSPA, TYKERB®, VCR, Vectibix™, Velban®, Velcade®, VePesid®, Vesanoide®, Viadur™, Vidaza®, Vinblastine, Vinblastine Sulfate, Vincasar Pfs®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vornostat, VP-16, Vumon®, Xeloda®, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolinza, Zometab®; radiopharmaceuticals such as: Carbon-11, Carbon-14, Chromium-51, Cobalt-57, Cobalt-58, Erbium-169, Fluorine-18, Gallium-67, Gold-198, Indium-111, Indium-113m, Iodine-123, Iodine-125, Iodine-131, Iron-59, Krypton-81m, Nitrogen-13, Oxygen-15, Phosphorous-32, Rhenium-186, Rubidium-82, Samarium-153, Selenium-75, Strontium-89, Technetium-99m, Thallium-201, Tritium, Xenon-127, Xenon-133, Yttrium-90; imaging agents such as Gadolinium, magnetite, manganese, technetium, I125, I131, P32, TI201, lopamidol, PET-FDG, (c) acromegaly drugs e.g. somatuline, lanreotide, octreotide, Sandostatin; antithrombotics e.g. bivalirudin, Angiomax, dalteparin, Fragmin, enoxaparin, Lovenox, Drotrecogin alfa (e.g. Activated), Xigris, heparin; assisted reproductive therapy compounds e.g. choriogonadotropin, Ovidrel, follitropin, alpha/beta; enzymes e.g. hyaluronidase, Hylenex; diabetes drugs e.g. exenatide, Byetta, glucagon, insulin, liraglutide, albiglutide, GLP-1 agonists, exendin or an exendin analog; compounds useful in diagnosis e.g. protirelin, Thyrel TRH, Thyphipnone, secretin (e.g. synthetic human), Chirhostim, thyrotropin (e.g. alpha), Thyrogen' erythropoiesis drugs e.g. Darbepoetin alfa, Aranesp, Epoetin alfa, Epogen, Eprex, drugs for the treatment of genetic defects e.g. pegademase, drugs for the treatment of growth failure e.g. Adagen, mecasermin, rinfabate, drugs for the treatment of cystic fibrosis e.g. Dornase alfa, Pulmozyme, drugs for the treatment of metabolic disorders e.g. Agalsidase beta, Fabrazyme, alglucosidase alpha, Myozyme, Laronidase, Aldurazyme, drugs for the treatment of genital wart intralesional e.g. Interferon alfa-n3, Alferon N, drugs for the treatment of granulomatous disease e.g. Interferon gamma-1b, Actimmune; drugs for the treatment of growth failure e.g. pegvisomant, Somavert, somatropin, Genotropin, Nutropin, Humatrope, Serostim, Protropin; drugs for the treatment of heart failure e.g. nesiritide, Natrecor; drugs for the treatment of hemophilia e.g. a coagulation factor e.g. Factor VIII, Helixate FS, Kogenate FS, Factor IX, BeneFIX, Factor VIIa, Novoseven, desmopressin, Stimat, DDAVP; hemopoetic drugs e.g. Filgrastim (G-CSF), Neupogen, Oprelvekin, Neumega, Pegfilgrastim, Neulasta, Sargramostim, Leukine; drugs for the treatment of hepatitis C e.g. Interferon alfa-2a, Roferon A, Interferon alfa-2b, Intron A, Interferon alfacon-1, Infergen, Peginterferon alfa-2a, Pegasys, Peginterferon alfa-2b, PEG-Intron; drugs for the treatment of HIV e.g. enfuvirtide, Fuzeon; Fabs e.g. Fab (antithrombin), Abciximab, ReoPro; monoclonal antibodies e.g. Daclizumab, Zenapax; antiviral monoclonal antibodies e.g. Palivizumab, Synagis; monoclonal antibodies for the treatment of asthma e.g. Omalizumab, Xolair; monoclonal antibodies for use in diagnostic imaging e.g. Arcitumomab, CEA-Scan, Capromab Pendetide, ProstaScint, Satumomab Pendetide, OncoScint CR/OV, Fabs for use in diagnostic imaging e.g. Nofetumomab, Verluma; immuno-suppressant monoclonal antibodies e.g. Basiliximab, Simulect, Muromonab-CD3, Orthoclone OKT3; monoclonal antibodies for the treatment of malignancy e.g. Alemtuzumab, Campath, Ibritumomab tiuxetan, Zevalin, Rituximab, Rituxan, Trastuzumab, Herceptin; monoclonal antibodies for the treatment of rheumatoid arthritis (RA) e.g. Adalimumab, Humira, Infliximab, Remicade; monoclonal antibodies for use as a radio-immuno-therapeutic e.g. Tositumomab and Iodine 1131, Tositumomab, Bexxar; drugs for the treatment of macular degeneration e.g. pegaptanib, Macugen; drugs for the treatment of malignancy e.g. Aldesleukin, Proleukin, Interleukin-2, Asparaginase, Elspar, Rasburicase, Elitek, Denileukin diftitox, Ontak, Pegaspargase, Oncaspar, goserelin, leuprolide; drugs for the treatment of multiple sclerosis (MS) e.g. Glatiramer acetate (e.g. copolymer-1), Copaxone, Interferon beta-1a, Avonex, Interferon beta-1a, Rebif, Interferon beta-1b, Betaseron; drugs for the treatment of mucositis e.g. palifermin, Kepivance; drug for the treatment of dystonia

e.g., neurotoxin, Botulinum Toxin Type A, BOTOX, BOTOX Cosmetic, Botulinum Toxin Type B, MYOBLOC; drugs for the treatment of osteoporosis e.g. teriparatide, Forteo; drugs for the treatment of psoriasis e.g. Alefacept, Amevive; drugs for the treatment of RA e.g. abatacept, Orencia, Anakinra, Kineret, Etanercept, Enbrel; thrombolytics e.g. Alteplase, Activase, recombinant tissue plasminogen activator (rtPA), Anistreplase, Eminase, Reteplase, Retavase, Streptokinase, Streptase, Tenecteplase, TNKase (tenecteplase), Urokinase, Abbokinase, Kinlytic; drugs for the treatment of osteoporosis e.g. calcitonin (e.g. salmon), Miacalcin, Fortical, drugs for the treatment of skin ulcers e.g. Becaplermin, Regranex, Collagenase, Santyl.

28. A nucleic acid encoding the polypeptide or fusion polypeptide of any of claims 1 to 14.

29. A vector comprising a nucleic acid according to claim 28.

30. A host cell comprising a nucleic acid according to claim 28 or a vector according to claim 29, preferably a eukaryote, preferably a yeast (such as *Saccharomyces cerevisiae*) or a mammalian cell (such as CHO or HEK) or a plant cell (such as rice).

31. A method of prophylaxis, treatment or diagnosis comprising administering a polypeptide, fusion polypeptide, conjugate, composition, associate, nanoparticle or microparticle or polynucleotide according to any of claims 1 to 14, 16 to 26 or obtainable by the method of claim 15 to a subject.

Figure 1

Hu_1_2_3	1	DAHKSEVAHRFKDLGEEHFKA	LVLI	AFAYQLQOCPFED	HVKLVNEVTEFAKTCVADES	AE
Hu_1_3	1	DAHKSEVAHRFKDLGEEHFKA	LVLI	AFAYQLQOCPFED	HVKLVNEVTEFAKTCVADES	AE
Hu_2_3	1	-----	-----	-----	-----	-----
Mac_mul	1	DTHKSEVAHRFKDLGEEHFKA	LVLI	AFAYQLQOCPFEEHVKLVNEVTEFAKTCVADES	AE	
Rat	1	EAHKSEIAHRFKDLGEOHFKA	LVLI	AFAYQLQKCPYEEH	IKLV	QEVTDFAKTCVADENAE
Mouse	1	EAHKSEIAHRYNDLGEQHFKA	LVLI	AFAYQLQKCSYDEHAKLV	QEVTDFAKTCVADESA	A
Hu_1_2_3	61	NCDKSLHTLFGDKLCTVATLRETYGEMADCCAQ	QEP	ERNECFLOHKDDNP	NLPRLV	RPEV
Hu_1_3	61	NCDKSLHTLFGDKLCTVATLRETYGEMADCCAQ	QEP	ERNECFLOHKDDNP	NLPRLV	RPEV
Hu_2_3	1	-----	-----	-----	-----	-----
Mac_mul	61	NCDKSLHTLFGDKLCTVATLRETYGEMADCCAQ	QEP	ERNECFLOHKDDNP	NLPPLV	RPEV
Rat	61	NCDKSLHTLFGDKLCATPKLR	DN	YGEIADCCAQ	QEP	ERNECFLOHKDDNP
Mouse	61	NCDKSLHTLFGDKLCATPNLRE	NY	GEIADCCTK	QEP	ERNECFLOHKDDNP
Hu_1_2_3	121	DVMCTAFHDNEETFLKKYLYE	IARRHPYFYAPELLFFAKRYKAA	FTECCQAADKAACLLP		
Hu_1_3	121	DVMCTAFHDNEETFLKKYLYE	IARRHPYFYAPELLFFAKRYKAA	FTECCQAADKAACLLP		
Hu_2_3	1	-----	-----	-----	-----	-----
Mac_mul	121	DVMCTAFHDNEETFLKKYLYE	IARRHPYFYAPELLFFAARYKAA	FTECCQAADKAACLLP		
Rat	121	EAMCTSFQENPTSF	LGHYLEVARRHPYFYAPELLYYAEKYNEVLT	QCCTESDKAACLT	P	
Mouse	121	EAMCTSFKENPTTF	MGHYLEVARRHPYFYAPELLYYAEQYNEILT	QCCAEADKESCL	T	P
Hu_1_2_3	181	KLDELDEGKASSAKQRLK	CASLQKFGERAFKAWAVARLSQ	RFPKAEFAEVSKLV	TDLT	K
Hu_1_3	181	KLDELDEGKASSA	-----	-----	-----	-----
Hu_2_3	1	--DELDEGKASSAKQRLK	CASLQKFGERAFKAWAVARLSQ	RFPKAEFAEVSKLV	TDLT	K
Mac_mul	181	KLDELDEGKASSAKQRLK	CASLQKFGDRAFKAWAVARLSQ	RFPKAEFAEVSKLV	TDLT	K
Rat	181	KLDVKEKALVAVRQRMK	SSMORFGERAFKAWAVARMSQ	RFPNAEFAEITTKLAT	DLTK	
Mouse	181	KLDGVKEKALVSSVRQRMK	SSMOKFGERAFKAWAVARLSQ	TFNADFAEITTKLAT	DLTK	
Hu_1_2_3	241	VHTECCHGDLLECADDRADLAKY	I	CENQDSISSKLKECC	KPLLEKSHC	IAEVENDEMPA
Hu_1_3	195	-----	-----	-----	-----	-----
Hu_2_3	59	VHTECCHGDLLECADDRADLAKY	I	CENQDSISSKLKECC	KPLLEKSHC	IAEVENDEMPA
Mac_mul	241	VHTECCHGDLLECADDRADLAKY	MCENQDSISSKLKECCDKPLLEKSHC	IAEVENDEMPA		
Rat	241	INKECCHGDLLECADDRADLAKY	MCENQATISSKLQACCDKPM	LQKSQCLAEIEH	DN	IP
Mouse	241	VNKECCHGDLLECADDRADLAKY	MCENQATISSKLQTCDDKPL	LKKAHCLSEVEH	DT	MP
Hu_1_2_3	301	DLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSV	V	LLLRLAKTYET	TLEK	C
Hu_1_3	195	-----	-----	-----	-----	-----
Hu_2_3	119	DLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSV	V	LLLRLAKTYET	TLEK	C
Mac_mul	301	DLPSLAADYVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSV	V	LLLRLAKAYEAT	LEK	C
Rat	301	DLPSIAADFVEDKEVCKNYAEAKDVFLGTFLYEYSRRHPDYSV	S	LLLRLAKKYEAT	LEK	C
Mouse	301	DLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSV	S	LLLRLAKKYEAT	LEK	C
Hu_1_2_3	361	CAAADPHECYAKVFDEFK	PLVEEPQNL	I	KQNC	ELFEQLGEYKFQ
Hu_1_3	195	-----	VEEPQNL	I	KQNC	ELFEQLGEYKFQ
Hu_2_3	179	CAAADPHECYAKVFDEFK	PLVEEPQNL	I	KQNC	ELFEQLGEYKFQ
Mac_mul	361	CAAADPHECYAKVFDEFQ	PLVEEPQNL	V	KQNC	ELFEQLGEYKFQ
Rat	361	CAEGDPACYGTVLAEFQ	PLVEEPKNLVKTNC	EL	Y	EKLGEYGFQ
Mouse	361	CAEANPPACYGTVLAEFQ	PLVEEPKNLVKTNC	DL	Y	EKLGEYGFQ

Figure 1 (continued)

Hu_1_2_3	421	PTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES
Hu_1_3	235	PTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES
Hu_2_3	239	PTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES
Mac_mul	421	PTLVEVSRNLGKVGAKCKKLPEAKRMPCAEDYLSVVLNRLCVLHEKTPVSEKVTKCCTES
Rat	421	PTLVEAARNLGRVGTKCCTLPEAQRLPCVEDYLSAILNRLCVLHEKTPVSEKVTKCCSGS
Mouse	421	PTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGS
↑		
500		
Hu_1_2_3	481	LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKEROIKKQTALVELVKHKPKAT
Hu_1_3	295	LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKEROIKKQTALVELVKHKPKAT
Hu_2_3	299	LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKEROIKKQTALVELVKHKPKAT
Mac_mul	481	LVNRRPCFSALELD EAYVPKAFNAETFTFHADMCTLSEKEKOVKKQTALVELVKHKPKAT
Rat	481	LVERRPCFSALTVDETYVPKEFKAETFTFHSDICTLPDEKEKQIKKQTALAEVLVKHKPKAT
Mouse	481	LVERRPCFSALTVDETYVPKEFKAETFTFHSDICTLPDEKEKQIKKQTALAEVLVKHKPKAT
↑		
500		
Hu_1_2_3	541	KEQLKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALGL
Hu_1_3	355	KEQLKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALGL
Hu_2_3	359	KEQLKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALGL
Mac_mul	541	KEQLKGVMDNF AAFVEKCKADDKEACFAEEGPKFVAASQAALA-
Rat	541	EDQLKTVMGDFAQFVDKCKAADKDNCFATEGPNLVARSKEALA-
Mouse	541	AEQLKTVMDDFAQFLDTCKAADKDTCFSTEGPNLVTRCKDALA-
↑		
550		
↑		
573		

Figure 2

Human	1	-----DA-HKSEVAHRFKDLGEEHFKA
Mouse	1	-----EA-HKSEIAHRYNDLGEQHFKG
Sheep	1	-----DT-HKSEIAHRFNDLGEENFOG
Rabbit	1	-----EA-HKSEIAHRFNDVGEEHFTG
Goat	1	-----DT-HKSEIAHRFNDLGEENFOG
Chimp	1	MNESSCCSTSLPAFGVSVLD SGHSSSAYS SRGV--FRDA-HKSEVAHRFKDLGEEHFKA
Macaque	1	-----MKWVTFISLLFLFSSAYS SRGV--FRDRT-HKSEVAHRFKDLGEEHFKA
Hamster	1	-----MKWVTFISLLFLFSSAYS SRGV--FRDA-HKSEIAHRFKDLGEQHFKG
Guinea_Pig	1	-----MKWVTFISLLFLFSSAYS SRGV--FRREA-HKSEIAHRFNDLGEQHFKG
Rat	1	-----MKWVTFISLLFLFSSAYS SRGV--FRREA-HKSEIAHRFKDLGEQHFKG
Cow	1	-----MKWVTFISLLFLFSSAYS SRGV--FRDRT-HKSEIAHRFKDLGEEHFKA
Horse	1	-----MKWVTFISLLFLFSSAYS SRGV--LRDRT-HKSEIAHRFNDLGEQHFKG
Donkey	1	-----MKWVTFISLLFLFSSAYS SRGV--LRDRT-HKSEIAHRFNDLGEQHFKG
Dog	1	-----MKWVTFISLLFLFSSAYS SRGV--VRREA-YKSEIAHRYNDLGEEHFKA
Chicken	1	-----MKWVTFISLLFLFSSAYS SRGV--LRDRT-HKSEIAHRYNDLKEETFKG
Pig	1	-----MKWVTFISLLFLFSSAYS SRGV--FRDRT-YKSEIAHRFKDLGEQHFKG

↑
(D1-Start)

Human	22	LVLIAFAQYLOQCPFEDHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Mouse	22	LVLIAFSQYLOQKCSYDEHAKLVQEVTDFAKTCVADESAENCDKSLHTLFGDKLCAIPNLR
Sheep	22	LVLIAFSQYLOQCPFEDHVKLNVKELTEFAKTCVADESHAGCDKSLHTLFGDELCKVATLR
Rabbit	22	LVLITFSQYLOQKCPYEEHAKLVKEVTDLAKACVADESAENCDKSLHDTFGDKICALPSLR
Goat	22	LVLIAFSQYLOQCPFEDHVKLNVKELTEFAKTCVADESHAGCDKSLHTLFGDELCKVATLR
Chimp	58	LVLVAFSAQYLOQCPFEDHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Macaque	46	LVLIAFSQYLOQCPFEEHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Hamster	46	LVLIAFSQYLOQKCPYEEHVKLNVNEVTDFAKTCVADESAENCDKSLHTLFGDKLCAIPNLR
Guinea_Pig	46	LVLITLSQHLQKSPFEEHVKLNVNEVTDFAKTCVADESAENCDKSLHTLFGDKLCAIPNLR
Rat	46	LVLIAFSQYLOQKCPYEEHVKLNVNEVTDFAKTCVADESAENCDKSLHTLFGDKLCAIPNLR
Cow	46	LVLIAFSQYLOQCPFEDHVKLNVNEVTEFAKTCVADESHAGCDKSLHTLFGDELCKVATLR
Horse	46	LVLIAFSQYLOQCPFEDHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Donkey	46	LVLIAFSQYLOQCPFEDHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Dog	46	LVLIAFSQYLOQCPFEDHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Chicken	49	VAMITFAQYLOQKCSYDEHAKLVQEVTDFAKTCVADESAENCDKSLHTLFGDKLCTVATLR
Pig	46	LVLIAFSQYLOQCPYEEHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCAIPNLR

Human	82	ETYGEMADCCAKQEPERNECFLOHKDDNPDL-PRLVRPEVDVMCTAFHDNEETFLKKYLY
Mouse	82	ENYGEADCCCTKQEPERNECFLOHKDDNPDL-PPFERPEAEAMCTSFKENPTTFMGHYLY
Sheep	82	ETYGDMADCCCKQEPERNECFLOHKDDNPDL-PKL-KPEPDTLCAEFKADEKKFWGKYLY
Rabbit	82	DTYGDVADCCCKQEPERNECFLOHKDDNPDL-PPFARPEADVLCKAFHDDEKAFFGHYLY
Goat	82	ETYGDMADCCCKQEPERNECFLOHKDDNPDL-PKL-KPEPDTLCAEFKADEKKFWGKYLY
Chimp	118	EKYGEMADCCAKQEPERNECFLOHKDDNPDL-PRLVRPEVDVMCTAFHDNEETFLKKYLY
Macaque	106	ETYGEMADCCAKQEPERNECFLOHKDDNPDL-PPLVRPEVDVMCTAFHDNEETFLKKYLY
Hamster	106	DSYGEMADCCAKQEPERNECFLOHKDDNPDL-PPFVRPEAEAMCTSFQENAVTFMGHYLY
Guinea_Pig	106	ETYGEADCCAKQEPERNECFLOHKDDNPDL-PPFERPEAEAMCTSFQENAVTFMGHYLY
Rat	106	DNYGEADCCAKQEPERNECFLOHKDDNPDL-PPFERPEAEAMCTSFQENAVTFMGHYLY
Cow	106	ETYGDMADCCCKQEPERNECFLOHKDDNPDL-PKL-KPEPDTLCAEFKADEKKFWGKYLY
Horse	106	ATYGEADCCCKQEPERNECFLOHKDDNPDL-PKL-KPEPDAQCAAFQEDPDKFLGKYLY
Donkey	106	ATYGEADCCCKQEPERNECFLOHKDDNPDL-PKL-KPEPDAQCAAFQEDPDKFLGKYLY
Dog	106	DKYGDMADCCCKQEPERNECFLOHKDDNPDL-PPLVAPPEADLCAAFQEDPDKFLGKYLY
Chicken	109	DSYGEMADCCSKADPERNECFLOHKDDNPDL-PPLVAPPEADLCAAFQEDPDKFLGKYLY
Pig	106	EHYGEMADCCCKQEPERNECFLOHKDDNPDL-PKL-KPEPDAQCAAFQEDPDKFLGKYLY

Figure 2 (continued)

Human	141	ETARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRLDEGKASSAKORLKC
Mouse	141	EVARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRORMKC
Sheep	140	EVARRHPYFYAPELLYYANKYNGVFOECCQAEADKACLLPKIDAMREKVLASSARORLRC
Rabbit	141	EVARRHPYFYAPELLYYAQYKAILTECCFAADKGACILTPKLDALLEGKSLISSAQERLRC
Goat	140	EVARRHPYFYAPELLYYANKYNGVFOECCQAEADKACLLPKIETMREKVLASSARORLRC
Chimp	177	EVARRHPYFYAPELLFFAERYKAAFTECCQAADKAACLLPKLDELRLDEGKASSAKORLKC
Macaque	165	EVARRHPYFYAPELLFFAARYKAAFTECCQAADKAACLLPKLDELRLDEGKASSAKORLKC
Hamster	165	EVARRHPYFYAPELLYYAEKYSAIMTECCGEADKAACILTPKLDALKEKALASSVNORLKC
Guinea_Pig	165	EVARRHPYFYAPELLYYAEKYKNALTECCFAADKAACILTPKLDALKEKALVSSAQORLKC
Rat	165	EVARRHPYFYAPELLYYAEKYNEVLTCCTESDKAACILTPKLDALKEKALVAAVRORMKC
Cow	164	ETARRHPYFYAPELLYYANKYNGVFOECCQAEADKACLLPKIETMREKVLASSARORLRC
Horse	164	EVARRHPYFYGPPELLFHAEYKADFTECCPADDKLACLIPKLDALKERILLSSAKERLKC
Donkey	164	EVARRHPYFYGPPELLFHAEYKADFTECCPADDKACLLIPKLDALKERILLSSAKERLKC
Dog	165	ETARRHPYFYAPELLYYAQYKGVFAECCQAADKAACLGPKIEALREKVLSSAKERLKC
Chicken	169	SVARRHPFLYAPATLSFAVDFEHALQSCCKESDVGACLDTKIEIVMREKAGVSVKQOYFC
Pig	164	ETARRHPYFYAPELLYYAIYKDVFECCQAADKAACLLPKIEHLREKVLSSAKORLKC

↑ ↑
 (D2-Start) (D1-End)

Human	201	ASLQKFGERAFAKAWAVARLSQRFPAKFAEVSKEIVTDLTKVHTECCCHGDLLECADDRADL
Mouse	201	SSMQKFGERAFAKAWAVARLSQTFPNADFAETTKLATDLTKVNKECCHGDLLECADDRADL
Sheep	200	ASIQKFGERAFAKAWAVARLSQKFPKADFTDVTKIVTDLTKVHKECCHGDLLECADDRADL
Rabbit	201	ASIQKFGDRAFKAWAVARLSQRFPAKADFTDTSKIVTDLTKVHKECCHGDLLECADDRADL
Goat	200	ASIQKFGERAFAKAWAVARLSQKFPKADFTDVTKIVTDLTKVHKECCHGDLLECADDRADL
Chimp	237	ASLQKFGERAFAKAWAVARLSQRFPAKFAEVSKEIVTDLTKVHTECCCHGDLLECADDRADL
Macaque	225	ASLQKFGDRAFKAWAVARLSQKFPKFAEFAEVSKEIVTDLTKVHTECCCHGDLLECADDRADL
Hamster	225	SSLQRFGERAFKAWAVARMSQKFPKADFAETTKLATDLTKLTEECCHGDLLECADDRADL
Guinea_Pig	225	ASLQKFGERAFAKAWAVARLSQKFPKFAEFAETSTIVTSLTKVTKECCHGDLLECADDRADL
Rat	225	SSMQRFGERAFKAWAVARMSQRFPAKFAEFAETTKLATDVTKINKECCHGDLLECADDRADL
Cow	224	ASIQKFGERAFAKAWAVARLSQKFPKFAEFAEVSKEIVTDLTKVHKECCHGDLLECADDRADL
Horse	224	SSFQNFGERAFKAWAVARLSQKFPKADFAEVSKEIVTDLTKVHKECCHGDLLECADDRADL
Donkey	224	SSFQKFGERAFAKAWAVARLSQKFPKADFAEVSKEIVTDLTKVHKECCHGDLLECADDRADL
Dog	225	ASLQKFGDRAFKAWAVARLSQRFPAKADFAETSKIVTDLTKVHKECCHGDLLECADDRADL
Chicken	229	GILKQFGDRVFCAROLIYLSQKYPKAPFSEVSKFVHDSIGVHKECCGDMVECDMDMARM
Pig	224	ASIQKFGERAFAKAWAVARLSQRFPAKADFTETSKIVTDLAKVHKECCHGDLLECADDRADL

Human	261	AKYICENQDSISSKLKECCDKPPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA
Mouse	261	AKYMCENQATISSKLOTCCDKPLLKKAHCLSVEHDTMPADLPATIAADFVEDQEVCKNYA
Sheep	260	AKYICDHQDATISSKLKECCDKPVLEKSHCIAEVDKDAVPENLPPLTADFAEDKEVCKNYQ
Rabbit	261	AKYMCHEHQBETISSHLKECCDKPILEKAHCITYGLHNDETPAGLPAAVEEFVEDKDVCKNYE
Goat	260	AKYICDHQDATISSKLKECCDKPVLEKSHCIAETDKDAVPENLPPLTADFAEDKEVCKNYQ
Chimp	297	AKYICENQDSISSKLKECCDKPPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA
Macaque	285	AKYMCENQDSISSKLKECCDKPPLLEKSHCIAEVENDEMPADLPSLAADYVESKDVCKNYA
Hamster	285	AKYMCENQASISSKLOACCDKPVLLKSHCLSEVENDDLPADLPSLAADFVEDKEVCKNYA
Guinea_Pig	285	AKYMCHEHQSISISSKLKECCVKPTLQKAHCILETQDELPTLPLDPAADFVEDKEVCKNFA
Rat	285	AKYMCENQATISSKLOACCDKPVLLQKSQCLAEIHDNIPADLPSIAADFVEDKEVCKNYA
Cow	284	AKYICDNQDTISSKLKECCDKPPLLEKSHCIAEVEKDAIPENLPPLTADFAEDKDVCKNYQ
Horse	284	AKYICEHQDSISGKLKACCDKPLLOKSHCIAEVEKEDDLPSDLPALAADFAEDKEICKHYK
Donkey	284	TKYICEHQDSISGKLKACCDKPLLOKSHCIAEVEKEDDLPSDLPALAADFAEDKEICKHYK
Dog	285	AKYMCENQDSISTKLKECCDKPVLEKSQCLAEVERDELPGDLPSLAADFVEDKEVCKNYQ
Chicken	289	MSNLCSQQDVFSGLTKDCCEKPIVERSOCLMAEFDEKPADLPSLIVEKYIEDKEVCKSFE
Pig	284	AKYICENQDTISSKLKECCDKPPLLEKSHCIAEAKRDELPAIDINPLEHDFVEDKEVCKNYK

Figure 2 (continued)

Human	321	EAKDVFLGMFLYEYARRHPDYSVLLLRLLAKTYETLEKCCAAADPHECYAKVFDEFKPL
Mouse	321	EAKDVFLGTFLYEYSRRHPDYSVLLLRLLAKKYEATLEKCCAEANPPACYGTVLAEFQPL
Sheep	320	EAKDVFLGSFLYEYSRRHPDYAVSVLLRLAKEYEATLEDCCAKEDPHACYATVFDKLKHL
Rabbit	321	EAKDLFLGKFLYEYSRRHPDYSVLLLRLLGKAYEATLEKCCATDDPHACYAKVLDEFQPL
Goat	320	EAKDVFLGSFLYEYSRRHPDYAVSVLLRLAKEYEATLEDCCAKEDPHACYATVFDKLKHL
Chimp	357	EAKDVFLGMFLYEYARRHPDYSVLLLRLLAKTYETLEKCCAAADPHECYAKVFDEFKPL
Macaque	345	EAKDVFLGMFLYEYARRHPDYSVLLLRLLAKAYEATLEKCCAAADPHECYAKVFDEFQPL
Hamster	345	EAKDVFLGTFLYEYARRHPDYSVLLLRLLAKKYEATLEKCCAEADPSACYGKVLDEFQPL
Guinea_Pig	345	EAKDVFLGTFLYEYSRRHPDYSIGMLLRLLAKGYEAKLEKCCAEADPHACYAKVFDELQPL
Rat	345	EAKDVFLGTFLYEYSRRHPDYSVLLLRLLAKKYEATLEKCCAEADPPACYGTVLAEFQPL
Cow	344	EAKDAFLGSFLYEYSRRHPDYAVSVLLRLAKEYEATLECCAKDDPHACYSTVFDKLKHL
Horse	344	DAKDVFLGTFLYEYSRRHPDYSVLLLRLLAKTYEATLEKCCAEADPPACYRTVFDQFTPL
Donkey	344	DAKDVFLGTFLYEYSRRHPDYSVLLLRLLAKTYEATLEKCCAEADPPACYATVFDQFTPL
Dog	345	EAKDVFLGTFLYEYARRHPDYSVLLLRLLAKYEATLEKCCATDDPPTCYAKVLDEFKPL
Chicken	349	AGHDAFMAEFVYEYSRRHPDYSIQILIMRIAKGYESTLEKCCCKTDNPAECYANAQEQLNQH
Pig	344	EAKHVFLGTFLYEYSRRHPDYSVLLLRLLAKIYEATLEDCCAKEDPPACYATVFDKQFQPL

Human	381	VEEPQNLIKONCELFEOIDGEYKFFONALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKKH
Mouse	381	VEEPKNLVKTNCDLFEKLGEYGFONAILVRYTOKAPQVSTPTLVEAARNLGRVGTCKCCTL
Sheep	380	VDEPQNLIKKNCELFEEKHGEYGFONALIVRYTRKAPQVSTPTLVEISRSLGKVGTKCCAK
Rabbit	381	VDEPKNLVKONCELFEOIDGEYNFONALLVRYTKKVPQVSTPTLVEISRSLGKVGSKCKKH
Goat	380	VDEPQNLIKKNCELFEEKHGEYGFONALIVRYTRKAPQVSTPTLVEISRSLGKVGTKCCAK
Chimp	417	VEEPQNLIKONCELFEOIDGEYKFFONALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKKH
Macaque	405	VEEPQNLVKONCELFEOIDGEYKFFONALLVRYTKKVPQVSTPTLVEVSRNLGKVGAKCKKL
Hamster	405	VEEPKNLVKANCELFEEKLGEYGFONALIVRYTOKAPQVSTPTLVEAARNLGKVGSKCCVL
Guinea_Pig	405	IDEPKKLVOONCELFEEKLGEYGFONALAVRYTOKAPQVSTPTLVEYARKLGSVGTCKCSL
Rat	405	VEEPKNLVKTNCELFEEKLGEYGFONAVLVRYTOKAPQVSTPTLVEAARNLGRVGTCKCCTL
Cow	404	VDEPQNLIKONCDQFEKLGEYGFONALIVRYTRKVPQVSTPTLVEVSRSLGKVGTRCCTK
Horse	404	VEEPKSLVKKNCDLFEEVGEYDFONALIVRYTKKAPQVSTPTLVEIGRTLKGKVGSRCKKL
Donkey	404	VEEPKSLVKKNCDLFEEVGEYDFONALIVRYTKKAPQVSTPTLVEIGRTLKGKVGSRCKKL
Dog	405	VDEPQNLVKTNCELFEEKLGEYGFONALLVRYTKKAPQVSTPTLVEVSRKLGKVGTKCKCK
Chicken	409	IKETQDVVKTNCDLLHHDGEADFLKSILIRYTKKMPQVPTDLLLETGKMTTIGTKCCQL
Pig	404	VDEPKNLIKONCELFEEKLGEYGFONALIVRYTKKVPQVSTPTLVEVARKLGLVGSRCKKR

↑ ↑
(D3-Start) (D2-End)

Human	441	PEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK
Mouse	441	PEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPK
Sheep	440	PESERMPCTEDYLSLILNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSDLTLDETYVPK
Rabbit	441	PEAERLPCVEDYLSVVLNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSALGPDETYVPK
Goat	440	PESERMPCTEDYLSLILNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSDLTLDETYVPK
Chimp	477	PEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK
Macaque	465	PEAKRMPCAEDYLSVVLNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSALELDEAVVPK
Hamster	465	PEAQRLPCVEDYLSAILNRVCLLHEKTPVSEQVTKCCTGSLVERRPCFSALPVDETYVPK
Guinea_Pig	465	PETERLSCTENYLALILNRLCLLHEKTPVSEKVTCCCTESLVNRRPCFSALHVDETYVPK
Rat	465	PEAQRLPCVEDYLSAILNRLCVLHEKTPVSEKVTCCCTGSLVERRPCFSALTVDETYVPK
Cow	464	PESERMPCTEDYLSLILNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSALTPDETYVPK
Horse	464	PESERLPCSENHLALALNRLCVLHEKTPVSEKVTCCCTSLAERRPCFSALELDEGYVPK
Donkey	464	PESERLPCSENHLALALNRLCVLHEKTPVSEKVTCCCTSLAERRPCFSALELDEGYTPK
Dog	465	PESERMSCAEDFLSVVLNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSGLEVDETYVPK
Chicken	469	GEDRRMACSEGYSIVLHDTGRKQETTPINDNVSOCCSOLYANRRPCFTAMGVDTKYVP
Pig	464	PEEERLSCAEDYLSVVLNRLCVLHEKTPVSEKVTCCCTESLVNRRPCFSALTPDETYVPK

Figure 2 (continued)

Human	501	EFNAETFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEOLKAVMDDFAAFVEKCKK
Mouse	501	EFKAETFTFHS DICTLPEKEKQIKKQATALAELVKHKPKATAEOLKTVMDFAQFLDTCKK
Sheep	500	PFDEKFTTFHADICTLPDTEKQIKKQATALVELLKHKPKATDEOLKTVMENFVAFVDKCCA
Rabbit	501	EFNAETFTFHADICTLPETERIKKQATALVELVKHKPHATNDOLKTVVGEFTALLDKCCS
Goat	500	PEDESFTTFHADICTLPDTEKQIKKQATALVELLKHKPKATDEOLKTVMENFVAFVDKCCA
Chimp	537	EFNAETFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEOLKAVMDDFAAFVEKCKK
Macaque	525	AFNAETFTFHADMCTLSEKEKQVKKQATALVELVKHKPKATKEOLKGVMDFNAAFVEKCKK
Hamster	525	EFKAETFTFHADICSLPEKEKOMKKQALVELVKHKPKATGFLRTVLGEFTAFLDKCKK
Guinea_Pig	525	PEHADSFTTFHADICTLPPEKEKQVKKQALVELVKHKPKASEEQMKTVMGDFAAFLKKCCD
Rat	525	EFKAETFTFHS DICTLPDKEKQIKKQATALAELVKHKPKATEDOLKTVMGDFACFVDKCKK
Cow	524	AFDEKLFTTFHADICTLPDTEKQIKKQATALVELLKHKPKATEEOLKTVMENFVAFVDKCCA
Horse	524	EFKAETFTFHADICTLPDEKQIKKQSALAEVLVKHKPKATKEOLKTVLGNFSAFVAKCCG
Donkey	524	EFKAETFTFHADICTLPDEKQIKKQSALAEVLVKHKPKATKEOLKTVLGNFSAFVAKCCG
Dog	525	EFNAETFTFHADICTLPPEKEKQVKKQATALVELLKHKPKATDEOLKTVMGDFGAFVEKCCA
Chicken	529	PFNPDMFSFDEKLCSAPAEEREVGOMKLLINLIKRPQMTTEEQIKTIADGFTAMVDKCKK
Pig	524	EFVEGTFTTFHADICTLPDEKQIKKQATALVELLKHKPHATEEOLRTVLGNFAAFVOKCCA

Human	561	ADDKETCFAEEGKKLVAASQAALGL--
Mouse	561	AADKDTCFSTEGPNLVTRCKDALA---
Sheep	560	ADDKEGCFVLEGPKLVASTQAALA---
Rabbit	561	AEDKEACFAVEGPKLVESSKATLG---
Goat	560	ADDKEGCFLLLEGPKLVASTQAALA---
Chimp	597	ADDKETCFAEEGKKLVAASQAALGL--
Macaque	585	ADDKEACFAEEGPKFVAASQAALA---
Hamster	585	AEDKEACFSEDGPKLVASSQAALA---
Guinea_Pig	585	ADNKEACFTEDGPKLVAKCOATLA---
Rat	585	AADKDNCFATEGPNLVARSKEALA---
Cow	584	ADDKEACFAVEGPKLVSTOTALA---
Horse	584	REDKEACFAEEGPKLVASSQLALA---
Donkey	584	AEDKEACFAEEGPKLVASSQLALA---
Dog	585	AENKEGCFSEEGPKLVAAAQAALV---
Chicken	589	QSDINTCFGEEGANLIVOSRATLIGIGA
Pig	584	APDHEACFAVEGPKFVIEIRILA---

↑
(D3-End)

Figure 3

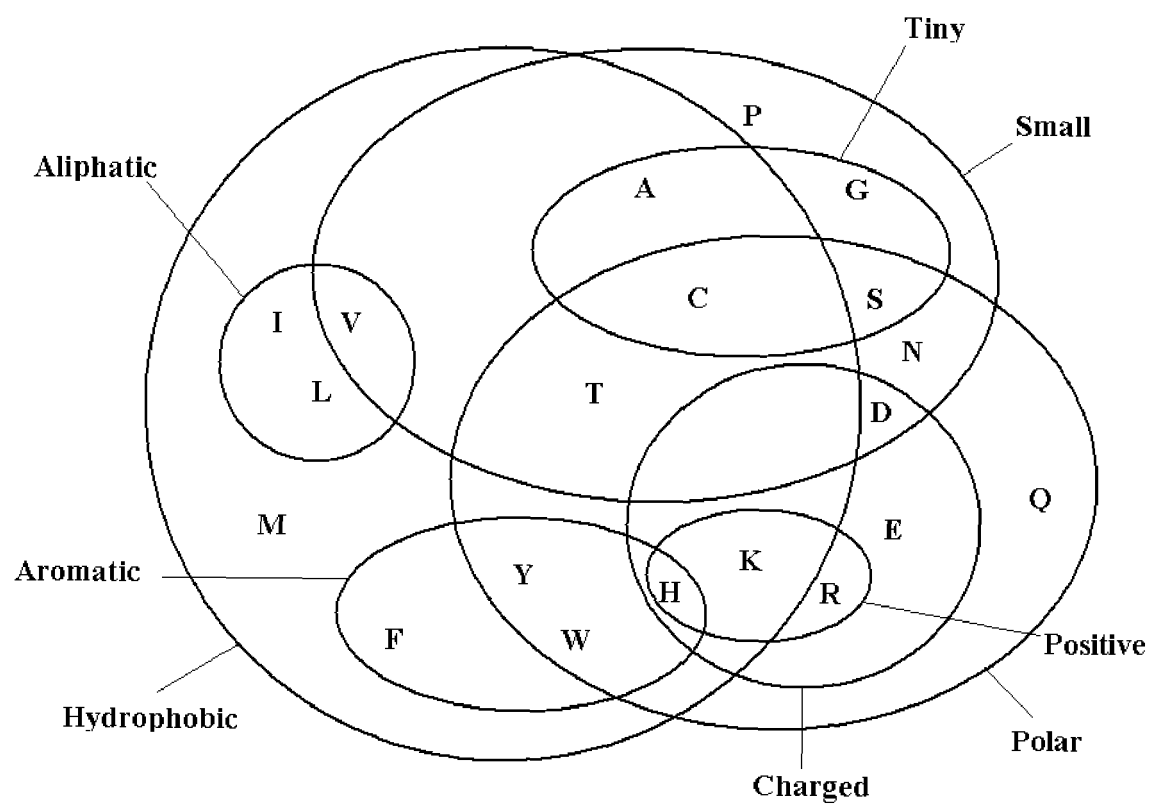


Figure 4

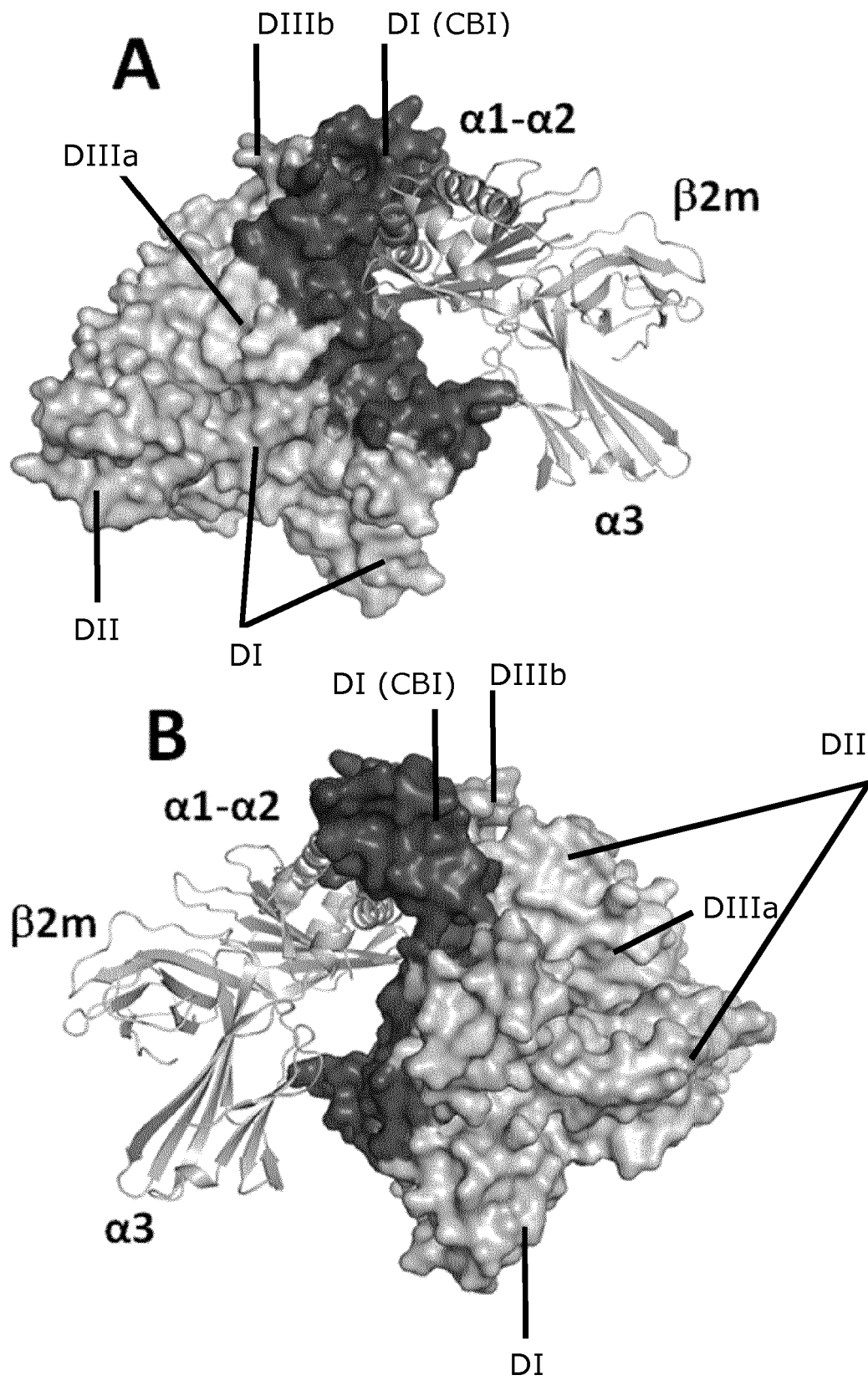


Figure 5

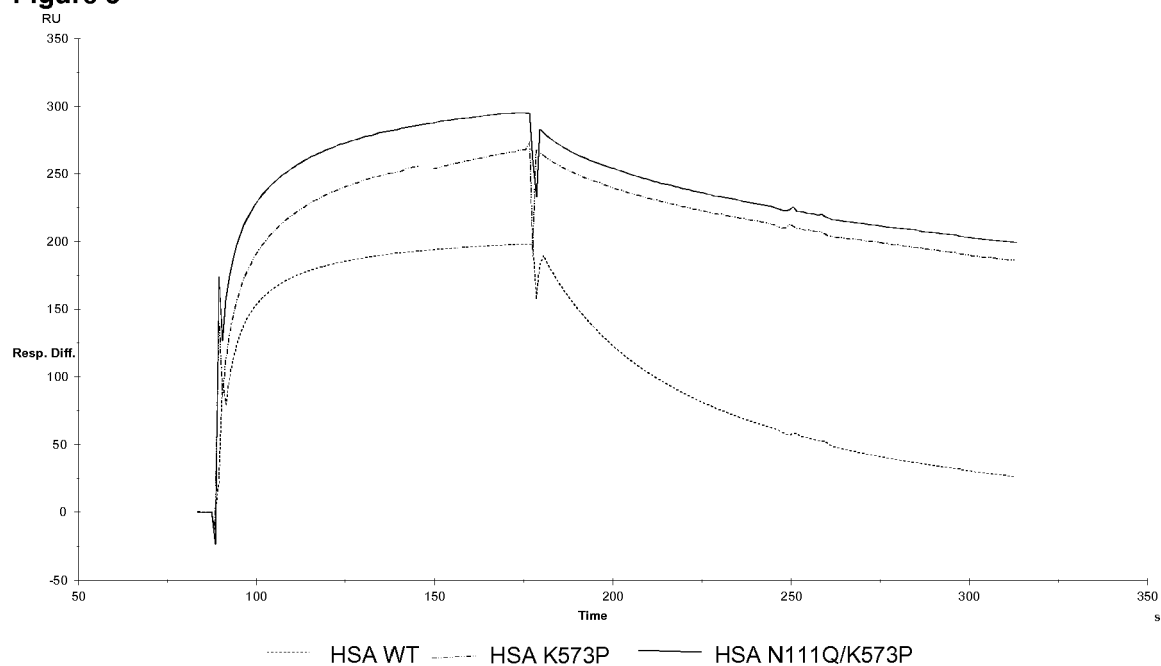
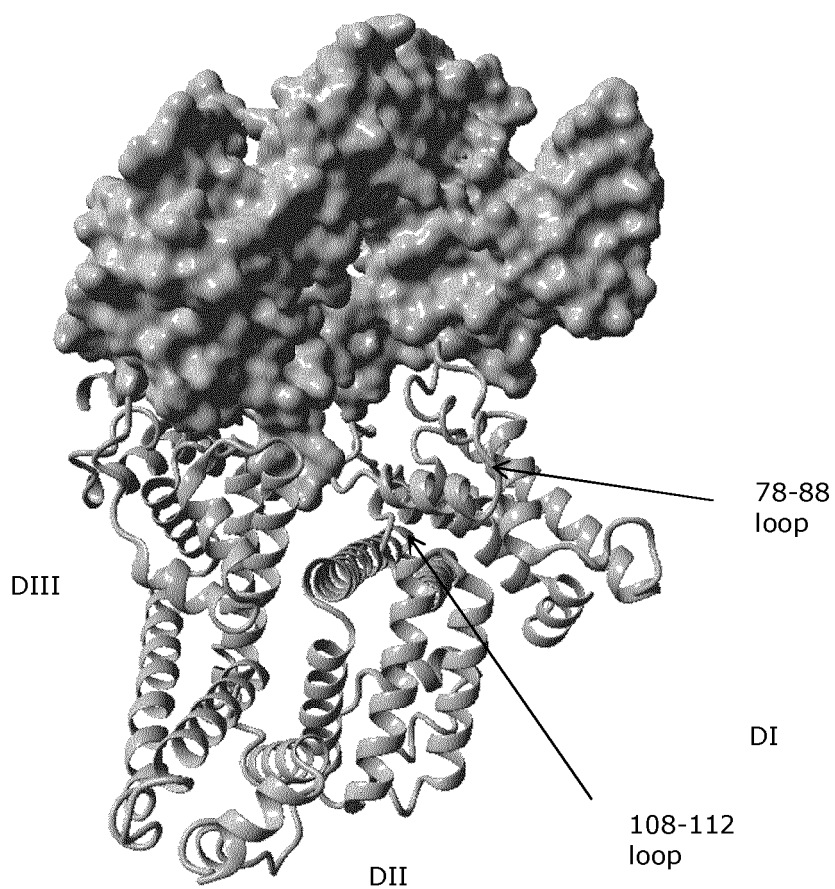


Figure 6



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